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TITLE: 2007 International Brain Mapping and Intraoperative Surgical Planning Society's (IBMISPS) Annual World Congress

PRINCIPAL INVESTIGATOR: Babak Kateb

CONTRACTING ORGANIZATION: International Brain Mapping & Intraoperative Surgical Planning Society (IBMISPS)
West Hollywood, CA 90046

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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
The third annual meeting of International Brain Mapping & Intra-operative Surgical Planning Society (IBMISPS) was held In Washington D:www.IBMISPS.Org. The Society is organized for the purpose of encouraging leading basic and clinical scientists who are interested or active in areas of Brain Mapping (BM) and intra-operative Surgical planning (ISP) to share their findings with other physicians and scientists across the disciplines. Currently, there is no combined conference on both subjects. This meeting intends to build a bridge between the two fields. The meeting has been organized by the board of directors and who will form the organizing committees: Search, Medical Education Committee, Program and Finance in collaboration with the local organizing committee who are listed on the program. The event did have significant clinical and basic science components. Thus, it was a multidisciplinary venue to explore and clarify a defined subject, problem, or area of knowledge related to BM and ISP with leaders in the field. The 5th annual meeting of IBMISPS is set for Aug 26-30, 2008 in Pasadena, CA. IBMISPS is also intended for the purpose of promoting the public welfare through the advancement of Intraoperative Surgical Planning and Brain Mapping, by a commitment to excellence in education, and by dedication to research and scientific discovery. The mission of the association will be achieved through a multi-disciplinary collaboration of government agencies, patient advocacy groups, educational institutes and private sector (industry) brought together in order to address issues and problems related to BM and ISP and implement new technologies to benefit patient care. We had specific scientific sessions on ranging from Image Guided Surgery, OR and Hospital of the future to nanomedicine & stem cell imaging ;All talks and abstracts that are presented at the meeting will be published on line and selected ones will be published in IBMISPS-NeuroImage.www.Elsevier.com

15. SUBJECT TERMS
Brain mapping, Cellular Imaging, Neuro-Navigation, Neurosurgery, Nanomedicine, OR & Hospital of the Future, Informatics, endoscopy, Biophotonics, Robotics, Brain Injury, PTSD, Spine

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2007 IBMISPS WORLD CONFERENCE
TATRC REPORT sf298

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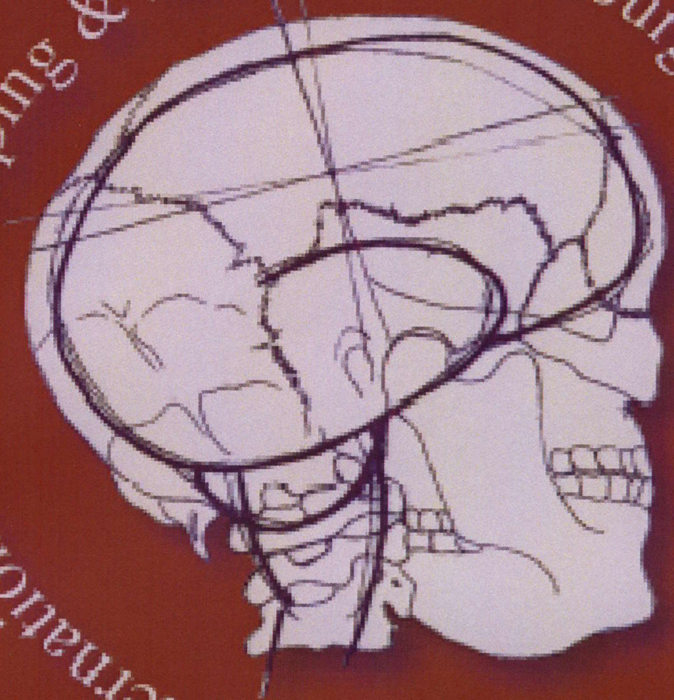
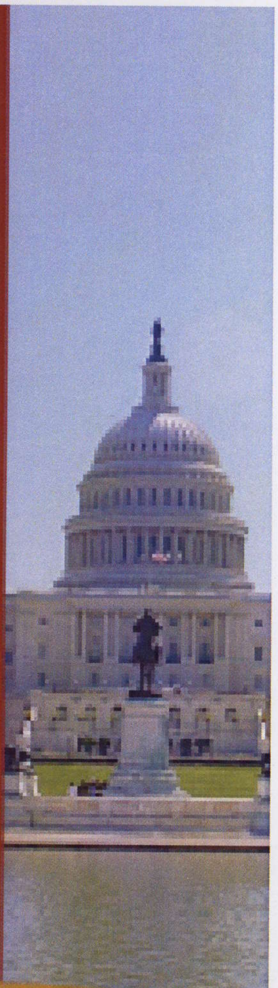
SEPTEMBER 6-8, 2007

International Brain Mapping & Intraoperative Surgical planning Society





4th Annual World Congress of IBMISPS

WASHINGTON PLAZA HOTEL
WASHINGTON DC
www.ibmisps.org

Welcoming Letter from the Founder:

Babak Kateb
Chairman of the Board, IBMISPS-Foundation
Founder and Executive Director, IBMISPS
Director of Research and Development
City of Hope national Cancer Center
Managing Editor IBMISPS-NeuroImage

I am pleased to welcome members of our society, scientists, physicians, and members of industry, academia and government to the 4th annual meeting of IBMISPS. We hold this meeting in Washington DC in order to build a broadly based multidisciplinary collaborative society focused on image guided therapy and intervention.

IBMISPS brings together a diverse scientific, medical and engineering community to discuss topics related to image guided therapy and intervention. Therefore, the society facilitates unprecedented interdisciplinary interactions amongst neurologists, neurosurgeons, rehabilitation medicine physicians, radiologists, electro physiologists, neuroscience, biophysicists, molecular biologists and other fields such as neural prosthetics.

IBMISPS is proud to announce its expansion to Japan, Germany, France, China, Korea, Brazil and australasia. The future is bright, we are now planning to introduce a unique interdisciplinary fellowship and travel awards for residents and fellows. IBMISPS is also planning to establish an strong foundation relations. In this regard we are and partnering with other foundations for humanitarian activities.

Thus, the member of the society not only could benefit from academic activities such as presenting their work in our annual meeting and publish it in our special issue of IBMISPS-NeuroImage but also could contribute to others through charitable and humanitarian work. The ultimate mission for IBMISPS is to bring technology and cutting edge research and medicine to those who needed the best. This includes our compatriots in the US and people of other nations. We are also proud to announce that the first IBMISPS-NeuroImage special issue is published.

I should thank the IBMISPS board of directors and organizing committee for their hard work on this congress and encourage you to submit your latest work to the 2007 IBMISPS-NeuroImage special issue. I look forward to meeting you in the next annual meeting in Los Angeles, California on
August 26-30, 2008.

Respectfully yours,

Babak Kateb,
Chairman of the Board, IBMISPS-Foundation
Founder and Executive Director, IBMISPS
Director of Research and Development
City of Hope national Cancer Center
Managing Editor IBMISPS-NeuroImage

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Managing Editor IBMISPS-NeuroImage Special Issue
Visiting Researcher at Caltech, CA
Director of Research & Development
Department of Neurological surgery & Brain Tumor Program
City of Hope National Cancer Center - USA

Board of Directors of IBMISPS and IBMISPS Foundation

MISSION STATEMENT

IBMISPS is a non-profit society organized for the purpose of encouraging basic and clinical scientists who are interested or active in areas of Brain Mapping (BM) and Intra-operative Surgical Planning (ISP) to share their findings with other physicians and scientists across the disciplines (i.e. neurosurgeons, radiologists, neurologists, biotechnologists, anthropologists, Engineers and neuroscientists).

This society is also intended for the purpose of promoting the public welfare through the advancement of Intra-operative Surgical Planning and Brain Mapping, by a commitment to excellence in education, and by dedication to research and scientific discovery.

The mission of the society will be achieved through a multi-disciplinary collaboration of government agencies, patient advocacy groups, educational institutes and private sector (industry) brought together in order to address issues and problems related to BM and ISP and to implement new technologies to benefit patient care.

EDUCATIONAL OBJECTIVES

The event will provide participants (physicians and allied health) with 29-34.8 hours of CME credit through Medical Educational Collaborative Corporation; a non-profit organization specialized for providing CME credit for medical conferences. Upon completion of the scientific meeting, participants should be able to:

- Identify new findings in Brain Mapping (BM) & Intra-operative Surgical Planning (ISP) most relevant to their own sub field (i.e. molecular imaging and or biophotonics)
- Describe the effect of the newly developed methods in BM and ISP
- Discuss and design the possible future research and developments in BM & ISP and assess the possible impact of such research and development on their own clinical and scientific work in the future
- Describe and assess the latest cutting-edge technological advancement in BM & ISP
- Explain ways to build a bridge between the two field, BM & ISP
- Discuss and describe governmental agencies roles in research and development of BM & ISP

CONGRESS CHAIRMAN & CO-CHAIRMEN

Babak KATEB Founder and Executive Director of IBMISPS - Chairman of the congress
Farzad MASSOUDI President of IBMISPS (2007-2008) - Co-Chairman of the congress
Warren GRUNDFEST Chairman of the Board (2007-2008) - Co-Chairman of the congress

4th Annual World Congress of IBMISPS
September 6 – 8, 2007
Washington USA

SPECIFIC PROGRAM TOPICS FOR SCIENTIFIC PAPERS

- General issues
- Operational issues
- Image guided systems
- Vascular & Blood flow imaging
- Intra-operative Surgical Planning & Image guided surgery/Therapy
- Brain Mapping (BM) and Intraoperative Surgical Planning (ISP) in Stereotactic Radiosurgery,
- Molecular and cellular imaging,
- Anatomy and histopathology,
- Nanoscience, Nanomedicine, genomics, computational genetics in BM
- 4D, Neuro-mathematics and bio-informatics,
- Neurophysiology,
- Functional brain mapping (fMRI, PET...),
- Endoscopy,
- Biophotonics,
- Neural Prosthesis & Robotics,
- Multi-modality imaging,
- Perfusion imaging, micromagnetic resonance imaging,
- Magnetic resonance Spectroscopic Imaging
- High-field and low field magnetic resonance,
- history of brain cartography,
- Ethical issues related to the BM & ISP,
- Transcranial Magnetic Stimulation and Magneto encephalographic
- Diffusion Tensor Imaging
- SPECT functional Brain Mapping
- Biomedical Informatics
- Cellular Imaging

LECTURES

- Scientific Exhibits (Posters)
- Practical sessions :
- Special focus sessions
  - Basic science
  - Clinical trials
  - Governmental regulation

Cutting edge research and development in BM and ISP

TARGET AUDIENCE

PHYSICIANS:
All physicians across the disciplines such as radiologists, neurologists, psychiatrists, internal medicine...

SURGEONS:
All surgeons across the disciplines such as neurosurgeons, cardiac and vascular surgeons etc...

OTHERS ENCOURAGED TO ATTEND

STUDENTS:
Undergraduate, graduate, post graduate and fellows

SCIENTIST AND ENGINEERS:
This includes all scientists from different disciplines such as aerospace engineers, biomedical engineers, neuroscientists and biotechnologists.

PATIENT ADVOCACY GROUPS:
Include all non profit patient advocacy groups in the world.

GOVERNMENT OFFICIALS AND AGENCIES:
NIH, NCI, WHO, FDA et. Set. Insurance Industry officials and member: Including all healthcare providers as well hospital CEOs and officials.

INDUSTRY:
Including all companies that are impacting the field.

ACCREDITATION

This activity has been planned and implemented in accordance with the Institute for Medical Quality and the California Medical Association's CME Accreditation Standards (IMQ/CMA) through the joint-sponsorship of CME Consultants and IBMISPS. CME Consultants is accredited by IMQ/CMA to provide continuing medical education for physicians. CME Consultants takes responsibility for content, quality and scientific integrity of this CME activity.

CME Consultants designates this educational activity for a maximum of 21.5 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity. This credit may also be applied to the CMA certificate in continuing medical education.

4th Annual World Congress of IBMISPS
September 6 – 8, 2007
Washington USA

INFORMATION - RESERVATION

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Tel: (310) 500-6196
Fax: (323) 654-3511
E-mail: contact@IBMISPS.org
Website: WWW.IBMISPS.ORG

AIRFARE

IBMISPS has made special arrangement with American Airline. A discount agreement has been completed with American Airlines and is valid 3-11 September, 2007 for travel to Washington, DC. (Dulles, Reagan or Baltimore airport) The Discount Code is A3397AD.

5% discount off the lowest applicable published air fare.
To make a discount reservation, please call AA Meeting Services Desk at 1-800-433-1790 from anywhere in the United States or Canada and refer to the discount Code.

The percentage discount can be booked on-line at www.AA.com for American Airlines and American Eagle flights only. For international originating
guests, please call your local reservations number and refer to the Discount Code

ABSTRACTS PUBLISHED IN SPECIAL ISSUE OF NEUROIMAGE

IBMISPS is accepting papers and abstract for its 4th annual world congress, which will be published in its special issue of NeuroImage
Submission guidelines and abstract form on the website: www.ibmisps.org.

VENUE OF THE CONGRESS

The 4th Annual World Congress will take place in Washington DC in the **Washington Plaza Hotel:** 10 Thomas Circle, NW - Washington, DC, Website **:** www.washingtonplazahotel.com

The Washington Plaza Hotel is located nearby: The White House, The Mall with a lot of free museums such as the National Gallery of Art (one of the world's prominent museums with European and American paintings, sculpture, works on paper, photographs, and decorative arts, collection galleries and Sculpture

LUNCHES & GALA DINNER

All the lunches (box lunches) will be served in the exhibition space.

Gala dinner Friday September 7, 2007:
The gala is designed to recognize individuals who have dedicated their lives to research, development, education and advancement of science, medicine and technology by the Board of Directors of IBMISPS.
The award committee will also present an award to an individual who has shown an extraordinary courage and dedication in facing a terminal illness and or helped with their relatives and or family members to fight back the illness.

There will be 4 different categories of awards:
- Pioneer in Medicine
- Excellence in Courage and Dedication:
- Pioneer in Healthcare Policy
- Pioneer in Technology

Cost: $50/person

Dress code Black Tie

4th Annual World Congress of IBMISPS
September 6 – 8, 2007
Washington USA

PROGRAM AT GLANCE

DAY ONE - THURSDAY SEPTEMBER 6, 2007

	FEDERAL HALL	ADAMS ROOM	NATIONAL HALL
08 :00 AM	Welcome & Introduction		
08 :20 AM	Key note Speaker		
08 :30 AM	Scientific Session 1 IMAGE GUIDED THERAPY		Exhibits 8.30 AM 5.30 PM
09.55 AM	Coffee break	Poster Session I 7.00 AM 12.00 AM	
10 :15 AM	Scientific Session 2 IMAGING INTRAOPERATIVE SURGICAL PLANNING		
11 :40 AM	Coffee break		
12 :00 AM	LUNCH TALK : TATRC		
12 :40 PM	Scientific Session 3 EMERGING CONCEPTS IN IMAGE GUIDED HERAPY:		
02 :05 PM	Tea Recess		
02 :25 PM	Scientific Session 4 ANIMAL & IN VIVO EXPERIMENTATION IN IMAGE	Poster Session II 1.00 PM 5.00 PM	
03.50 PM	Coffee Break		
04 :10 PM	Scientific Session 5 CELLULAR IMAGING & NANOMEDICINE		
05 :55 PM	End of sessions		
06.00 PM	BOARD OF ADVISORS & DIRECTORS MEETING		

DAY ONE • SEPTEMBER 6, 2007

SCIENTIFIC SESSIONS

Time	Session	Exhibit / Poster
8:00 – 8:20 AM	*Official* Welcome & Introduction by Chair: Babak KATEB, Co-Chair: Farzad MASSOUDI (President of IBMISPS, 2007-2008) Co-Chair: Warren GRUNDFEST (Past president of IBMISPS, 2006-2007)	EXHIBIT HALL 8:00 AM– 5:55 PM
8:20 – 8:30 AM	Key Note Speaker: **The Honorable Senator John EDWARDS** (TENTATIVE)	
	Scientific Session 1: Image Guided Therapy	
8:30 – 8:45 AM	**Chair: Babak KATEB** Director of Research & Development Brain Tumor Program Department of Neurosurgery, City of Hope National Cancer Center, Founder and Executive Director of IBMISPS, CEO and Chairman of the Board of Directors, IBMISPS Foundation *Nanoneurosurgery and Image Guided Therapy*	POSTER SESSION I 9:00 – 12:00 PM
8:45 – 9:00 AM	**Keyvan FARAHANI** Acting Branch Chief Cancer Imaging Program National Cancer Institute *Funding Opportunities in Image-Guided Oncological Interventions*	
9:00 – 9:15 AM	**John HALLER** Liaison for International Activities National Institute of Biomedical Imaging and Bioengineering NIBIB/NIH/DHHS *NIBIB/NIH Programs for Image-Guided Surgery*	

9:15 – 9:30 AM	**Co-chair:** **Walter J. KORSHETZ** Deputy Director, Office of the Director National Institutes of Health National Institute of Neurologic Disorders and Stroke NIH/NINDS *Progress and Challenges in Mapping Stroke*	
9:30 – 9:45 AM	**Christian MACEDONIA** Lieutenant Colonel, Medical Corps, US Army Chief of Research Operations Telemedicine and Advanced Technology Research Center U.S. Army Medical Research and Materiel Command (MRMC) Associate Professor of Ob/Gyn, Military and Emergency Medicine Uniformed Services University *Terra Incognita: Imaging Research Opportunities Directed Toward a Better Understanding of the Assembly of the Human Brain*	
9:45 – 9:55 AM	Q/A	
9:55 - 10:15 AM	Coffee Break	
	Scientific session 2: ***Imaging; Intra-operative Surgical Planning***	
10:15 – 10:30 AM	**Chair:** **Ferenc A. JOLESZ** B. Leonard Holman Professor of Radiology Vice Chairman for Research Director, Division of MRI and Image Guided Therapy Program Department of Radiology Brigham and Women's Hospital Harvard Medical School *MRI guided FUS of the Brain*	
10:30 – 10:45 AM	**Chair:** **Jean Jacques LEMAIRE** *University Hospital of Clermont-Ferrand* *Professor of Neurosurgery (ESPRI/INSERM),* *Auvergne University, France* *Toward Guidelines for Image Guided Surgeries*	

10:45 – 11:00 AM	**Mitsunori MATSUMAE** Professor of Neurosurgery Department of Neurosurgery Tokai University School of Medicine, Japan *Operating Room of the Future: Fully Functional MR-Compatible Flexible Operating Table Resolves the Neurosurgeon's Dilemma Over Use of Intraoperative MRI*	
11:00 – 11:15 AM	**Shoichiro ISHIHARA** Associate Professor, Department of Neurosurgery Chief of Division of Endovascular Neurosurgery, Stroke Center, International Medical Center, Saitama Medical University, Japan *Operating Room of the Future:* *A Integrated Hybrid Operating Room for Neurosurgery*	
11:15 – 11:30 AM	**Thilo HOELSCHER** Assistant Professor Department of Radiology University of California San Diego, School of Medicine *Advanced Intraoperative Brain Ultrasound:* *Current Technologies and Potential Applications*	
11:30 – 11:40 AM	Q/A	
11:40 – 12:00 PM	Coffee Break	
12:00 – 12:30 PM	**Key Note Speaker:** **Ken CURLEY** Chief Scientist, Neuroscience Portfolio Manager, Telemedicine and advance technology Research Center (TATRC),US Army medical Research and Material Command (MRMC), Assistant Professor of Military and Emergency Medicine, Surgery and Biomedical Informatics, Uniformed Services University of the Health Sciences (USUHS) ***Neuroscience Research at the U.S. Army Telemedicine and Advanced Technology Research Center:*** ***Opportunities for Engaging the Brain Mapping and Intraoperative Surgical Planning Communities***	
12:30 – 12:40 PM	Q/A	

Scientific session 3: Emerging Concepts in Image Guided Therapy: Vascular and Blood Flow Imaging, Human Brain Machine Interface, Biophotonics and Simulation

POSTER SESSION II
1:00 – 5:00 PM

12:40 – 12:55 PM

Chair:
Elizabeth BULLITT
Van Weatherspoon Jr. Professor of Surgery,
Director of CASILab,
University of North Carolina,
Glioma and Vessel Shape as Monitored by Magnetic Resonance Angiography (MRA)

12:55 – 1:10 PM

Dawn TAYLOR
Assistant Professor of Biomedical Engineering, Case Western Reserve University
Research Scientist, Cleveland VA Medical Center
Changes in Neural Activity Patterns with Use of Brain-Machine Interfaces

1:10 – 1:25 PM

Andreas POMMERT
VOXEL-MAN Group University Medical Center Hamburg-Eppendorf
Navigation Support Through Preoperative Simulation of Cranial Interventions

1:25 – 1:40 PM

Malisa SAMTINORANONT
Assistant Professor
Department of Mechanical and Aerospace Engineering,
University of Florida
Computational Transport Models of Convection-Enhanced Delivery

1:40 – 1:55 PM

Co-chair :
Richard D. BUCHOLZ
Director, Division of Neurosurgery
KR Smith Endowed Professor of Neurosurgery
Saint Louis University School of Medicine, USA
Experience with DexVue: A Hybrid Surgical Planning, Simulation, and Navigation System

1:55 – 2:05 PM

Q/A:

2:05 – 2:25 PM

Tea Recess

Scientific session 4: Animal Modeling and In vivo experimentation in Image Guided Therapy	
2:25 – 2:40 PM	**Chair:** **Elaine L. BEARER,** Professor, Department of Pathology and Laboratory Medicine Warren Alpert Medical School of Brown University *Emerging Concepts in Neuroimaging: Animal models, plasticity and circuitry*
2:40 – 2:55 PM	**Co-Chair:** **Thomas WOOLSY** George H. and Ethel R. Bishop Scholar in Neuroscience, Professor of Experimental Neurosurgery, Experimental Neurology, Anatomy and Neurobiology, Cell Biology and Physiology and Biomedical Engineering; Washington University School of Medicine *Imaging for Animal Models of Brain Disease*
2:55 – 3:10 PM	**Jean WRATHALL** Professor, Dept of Neuroscience Georgetown University School of Medicine *Animal Models of Spinal Cord Injury and Regeneration: New Opportunities for Pharmacologic Interventions*
3:10 – 3:25 PM	**Russell E. JACOBS,** Member of the Beckman Institute Caltech Brain Imaging Center *Looking Deeper into Vertebrate Brain Development*
3:25 – 3:40 M	**Inseob HAHN** Research Scientist NASA/JPL, California Institute of Technology, Pasadena, CA *Development of Low-Field SQUID MRI Prototype System: In-Vivo MRI Results and Intraoperative Imaging Implications*
3:40 – 3:50 PM	Q/A:
3:50 – 4:10 PM	Coffee Break

	Scientific session 5: Cellular Imaging and NanoMedicine
4:10 – 4:25 PM	**Chair :** **Ali ARBAB** Associate Scientist Radiology Research Henry Ford Health System *Cellular MRI for the Detection of Glioma*
4:25 – 4:40 PM	**Co-Chair :** **Jeff BULTE** Professor of Radiology Professor of Chemical and Biomolecular Engineering Director, Cellular Imaging Section, Institute for Cell Engineering; Russell H. Morgan Department of Radiology and Radiological Science Division of MR Research Johns Hopkins University School of Medicine *Cellular Neuroimaging*
4:40 – 4:55 PM	**Mike MODO** Wolfson Lecturer in Stem Cell Imaging The James Black Centre, Institute of Psychiatry Kings College London, *MRI-guided Transplantation of Neural Stem Cells in Stroke*
4:55 – 5:10 PM	**Piotr WALCZAK** Research Associate The Russell H. Morgan Department of Radiology and Radiological Science Division of MR Research Institute for Cell Engineering Johns Hopkins University School of Medicine *Towards Developing Cell-Based Neurorepair Strategies - Monitoring Status of Transplanted Cells in Vivo with Bioluminescence and MRI*
5:10 – 5:25 PM	**Stanley FRICKE** Associate Professor, Dept. of Neuroscience Director, Small Animal Imaging Laboratory (SAIL) Georgetown University School of Medicine *Magnetic Nanoparticles for CNS Cell Tracking*
5:25 – 5:55 PM	Q/A and Break
6:00 – 9:00 PM	**BOARD Of ADVISORS AND DIRECTORS Meeting**

Board of Director's Meeting
6:00 – 9:00 PM

4th Annual World Congress of IBMISPS
September 6 – 8, 2007
Washington USA

PROGRAM AT GLANCE
DAY TWO - FRIDAY SEPTEMBER 7, 2007

Time	FEDERAL HALL
08 :00 AM	Key Note speaker
08 :30 AM	Scientific Session 6 STEREOTACTIC RADIOSURGERY
10 :00 AM	Coffee break
10 :05 AM	Scientific Session 7 RADIATION ONCOLOGY
11 :30 AM	Key Note speaker
12.00 PM	Coffee break
12.20 PM	Scientific Session 8 MULTI-MODALITY IMAGING
01 :45 PM	Tea recess
02 :05 PM	Scientific Session 9 NEW HORIZON
03 :30 PM	Coffee Break
03 :50 PM	Scientific Session 10 BIOMEDICAL INFORMATICS
05 :05 PM	End of sessions

ADAMS ROOM	NATIONAL HALL
Poster Session I 7.00 AM 12.00 AM	Exhibits 8.30 AM 5.30 PM
Poster Session II 1.00 PM 5.00 PM	

06 :30 Cocktail Party

8 :30 Black Tie GALA

DAY TWO • SEPTEMBER 7, 2007 SCIENTIFIC SESSIONS

Time	Session	Parallel events
8:00 – 8:30 AM	**Key Note speaker:** **Recipient of the 2007 IBMISPS Pioneer in Medicine Award:** **Richard FRACKOWIAK** Vice-provost for Special Projects, Professor, Wellcome Department of Imaging Neuroscience at the Institute of Neurology, Professor of Neurology University College of London President, British Neuroscience Association ***Modern Non-Invasive Investigation of Human Brain Structure and Function In Genetic and Neurodegenerative Disease***	POSTER SESSION I 7:00 – 12:00 PM EXHIBIT HALL 8:00 AM – 5:05 PM
	Scientific Session 6: Stereotactic –Radiosurgery	
8:30 – 8:45 AM	**Chair:** **Farzad MASSOUDI** Clinical Assistant Professor of Neurosurgery David Geffen-UCLA School of Medicine, Massoudi Medical Group	
8:45 – 9:00 AM	**Co-Chair:** **Antonio A. F. DE SALLES** Professor of Neurosurgery, Head of Stereotactic Radiosurgey David Geffen-UCLA School of Medicine *Mapping in Radiosurgery*	
9:00 – 9:15 AM	**Reinhard SCHULTE** Assistant Professor Radiation Medicine Loma Linda School of Medicine, Proton Therapy *Proton Radiosurgery: Past, Present and Future*	
9:15 – 9:30 AM	**Shearwood Mc CLELLAND III** Resident Department of Neurosurgery, University of Minnesota Medical School, Minneapolis *Typical Variations of Subthalamic Electrode Location Do Not Predict Limb Motor Function Improvement in Parkinson's Disease*	

Time	Session	
9:30 – 9:45 AM	**David LARSON** Professor of Radiation Oncology and Neurological Surgery , Director, CyberKnife Radiosurgery Program Co-Director, Gamma Knife® Radiosurgery Program Principal Investigator, Brain Tumor Research Center , Clinical Chief, Department of Radiation Oncology, Long Hospital, Program Member, UCSF Comprehensive Cancer Center, UCSF School of Medicine Advances in Gamma Knife Radiosurgery	
9:45 – 10:00 AM	Q/A	
10:00 – 10:05 AM	Coffee Break	
	Scientific Session 7: ***Radiation Oncology and Special topics***	
10:05 – 10:20 AM	**Chair :** **Erik H. RADANY** Associate Professor of Radiation Oncology City of Hope National Cancer Center, Duarte, CA *Helical Tomotherapy for the Delivery of Stereotactic Brain Irradiation*	
10:20 – 10:35 AM	**An LIU** Assistant Professor Department of Radiation Oncology City of Hope Cancer Center, Duarte, CA *A Multi-Center Consortium Study of Competing Platforms for Stereotactic Brain Irradiation*	
10:35 – 10:50 AM	**Kathryn McMILLAN** Department of Radiology, Vanderbilt, Nashville, Tennessee, USA *Multi-Parametric Imaging in Brain Metastases: Measuring Cognitive and Overall Response to Whole Brain Radiation*	

10:50 – 11:15 AM	**Special Topic** **Ramesh RAMAN** Senior/Expert Reviewer/Medical Officer Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), Division of Neurology Drug Products (DNP), *A Focused Approach to the Clinical Development of Imaging Drugs*
11:20 – 11:30 AM	Q/A
11:30 – 12:00 PM	**Key Note Speaker:** **Helen ROUTH** General Manager, Philips Research North America New Developments in Image Guided Therapy
12:00 – 12:20 PM	Coffee Break
	Scientific Session 8: ***Multi-Modality Imaging***
12:20 – 12:35 PM	**Chair:** **Alexandra GOLBY** Assistant Professor of Neurosurgery, Associate Surgeon, Brigham and Women's Hospital Director of Image Guided Neurosurgery, Brigham and Women's Hospital, Harvard Medical School *Advanced white Matter Tractography*
12:35 – 12:50 PM	**Co-Chair:** **Shouleh NIKZAD** Head of Nanoscience and Advanced Detector Arrays Group, Jet Propulsion Laboratory (JPL) *UV-Imaging*
12:50 – 1:05 PM	**Susumu MORI** Professor, Department of Radiology, Johns Hopkins University School of Medicine *Reconstruction of White Matter Using Diffusion Tensor Imaging and Its Application to Neurosurgery*

		POSTER SESSION II 1:00 – 5:00 PM
1:05 – 1:20 PM	**Peter VAN ZIJL** Professor of Radiology, Johns Hopkins University School of Medicine Director, F.M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Research Institute *New MRI Technologies with Clinical Potential*	
1:20 – 1:35 PM	**Barry KOSOFSKY** Chief, Division of Pediatric Neurology New York Presbyterian Hospital (Cornell Campus) Goldsmith Professor of Pediatrics, Neurology, and Neuroscience Weill-Cornell Medical College *Application of high resolution structural imaging to brain development*	
1:35 – 1:45 PM	Q/A:	
1:45 – 2:05 PM	Tea Recess	
	Scientific Session 9: ***New Horizon; Biomedical Engineering, Cancer Modeling, Virtual Reality and Simulation in Image Guided Therapy***	
2:05 – 2:20 PM	**Chair:** **David MOORE** Deputy Director for Research, Defense and Veterans Brain Injury Center, Walter Reed Army Medical Center *Computational Biology, Primary Blast Injury and the Central Nervous System*	
2:20 – 2:35 PM	**Amy RYAN** Jet Propulsion Laboratory/NASA *Electronic Nose*	
2:35 – 2:50 PM	**Co-Chair :** **Mike CHEN** Assistant Professor, Department of Neurosurgery City of Hope National Cancer Center, CA ***In-vitro Analysis of Cells and Tissues using the Electronic Nose***	

2:50 – 3:05 PM	**Simon K. WARFIELD** Associate Professor of Radiology, Children Hospital Boston, MA, USA *Algorithms for Planning for Pediatric Neurosurgery*	
3:05 – 3:20 PM	**Vittorio CRISTINI** Associate Professor School of Health Information Sciences, The University of Texas Health Science Center, Houston Computational Modeling Identifies Morphologic Predictors of Tumor Invasion	
3:20 – 3:30 PM	Q/A:	
3:30 – 3:50 PM	Coffee Break:	
	Session 10 ***Biomedical Informatics: Grid Technology-New Generation of On-line Data Transfer and IT for the Life Sciences***	
3:50 – 4:05 PM	**Chair :** **Stephan G. ERBERICH** Director of Functional Imaging & Biomedical Informatics, Department of radiology, Children Hospital Los Angeles, Assistant Professor of Radiology and Biomedical Engineering, Keck School of Medicine & Viterbi School of Engineering, University of Southern California *Globus MEDICUS - Service Oriented Architecture for Radiological Images*	
4:05 – 4:20 PM	**Co-Chair :** **Carl KESSELMAN** Director, Center for Grid Technologies, Information Science Institute Research Professor of Computer Science, Viterbi School of Engineering, University of Southern California *General Grid Technology*	

4:20 – 4:35 PM

John WILBANK
Executive Director,
Science and Creative Commons,
Novel methods for sharing and integrating web-based data

4:35 – 4:50 PM

Mary KRATZ
Executive Vice President, Health-Grid US Alliance
Advisor to the Director of US Army and Material Command Center (USAMCC),
Telemedicine Advanced Technology Research Center (TATRC)
Hospital of the Future

4:50 – 5:05 PM

Jonathan C. SILVERSTEIN
Assistant Professor, Surgery and Radiology,
Associate Director , Computation Institute, Argonne National Laboratory and
The University of Chicago
HealthGrid :
Applications of Grid Technologies to Biomedicine

~ Awards Banquet ~
Friday, September 7, 2007
6:30 – 8:00 PM
Coktail
8:30 – 11:00 PM
Dinner and Award

PROGRAM AT GLANCE
DAY THREE – SATURDAY SEPTEMBER 8, 2007

Time	FEDERAL HALL	ADAMS ROOM	NATIONAL HALL
08 :45 AM	Program Review		
09 :15 AM	Scientific Session 11 INTERDISCIPLINARY NEUROSCIENCE	Poster Session I 7.00 AM 12.00 AM	Exhibits 8.30 AM 5.30 PM
10 :40 AM	Coffee break		
11.00 AM	Scientific Session 12 PSYCHIATRY AND BRAIN INJURY		
12 :20 PM	Key Note speaker		
01 :00 PM	Scientific Session 13 SPINE INSTRUMENTATION, INJURY, REGENERATION AND ADVANCEMENTS	Poster Session II 1.00 PM 5.00 PM	
02.25 PM	Tea recess		
02 :45 PM	Scientific Session 14 NEUROPHYSIOLOGY AND FUNCTIONAL NEUROSURGERY		
04.10 PM	Coffee Break		
04.30 PM	Scientific Session 15 BRAIN INJURY AND TRAUMA		
05 :45 PM	Officials closing remarks		

DAY THREE • SEPTEMBER 8, 2007 — SCIENTIFIC SESSIONS

8:45 – 9:15 AM

Program Review by Congress Co-chairs

Key Note

Scientific Session 11: Interdisciplinary Neuroscience

9:15 – 9:30 AM

Chair:
Fraser HENDERSON (No talk)
Co-Chair:
Amir VOKSHOOR (No talk)

Daniel DJAKIEW
Professor of Biochemistry,
Molecular Biology and Cellular Biology
Georgetown University School of Medicine
The role of p75 Neurotrophin Receptor in Oncology

EXHIBIT HALL
9:00 – 5:45 PM

POSTER SESSION I
9:00 – 12:00 PM

9:30 – 9:45 AM

Kristi SCHMIDT
Fellow,
Department of Neurosurgery
Department of Neurosurgery
Georgetown University School of Medicine
Spinal Cord Stress Injury Assessment (SCOSIA):
Clinical Results and Validation

9:45 – 10:00 AM

Perry RICHARDSON
Associate Professor of Neurology;
Residency Program Director,
Department of Neurology,
George Washington University
School of Medicine
A CASE REPORT:
Tumefactive Multiple Sclerosis: Comparative Imaging Technique

10:00 – 10:15 AM

Kenneth H. WONG
Assistant Professor ISIS Center,
Georgetown University School of Medicine
Wearable Sensor Arrays for Blast and Acceleration-Induced Injury

10:15 – 10:30 AM	**Special Topic** **Ramesh RAMAN** Senior/Expert Reviewer/Medical Officer Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), Division of Neurology Drug Products (DNP), *A Focused Approach to the Clinical Development of Imaging Drugs*	
10:30 – 10:40 AM	Q/A:	
10:40 – 11:00 AM	Coffee Break	
	Scientific Session 12: Psychiatry and Brain Injury	
11:00 – 11:15 AM	**Chair:** **Stephen LAWRIE** (Hons) MRCPsych MPhil Sackler Senior Clinical Research Fellow & Reader in Psychiatry Division of Psychiatry, University of Edinburgh Royal Edinburgh Hospital *Imaging Genetic Effects in Schizophrenia*	
11:15 – 11:30 AM	**Doug BREMNER** Professor of Psychiatry and Radiology, Emory University School of Medicine *Brain Imaging of Childhood Abuse Related Posttraumatic Stress Disorder*	
11:30 – 11:45 AM	**Michael J. ROY** Colonel, Medical Corps, U.S. Army Director, Division of Military Internal Medicine Professor of Medicine Uniformed Services University of the Health Sciences *The ViRTICo-PB Trials: Virtual Reality Therapy and Imaging in Combat Veterans with PTSD and Traumatic Brain Injury*	
11:45 – 12:00 PM	**Michael W. WEINER** Director, Center for Imaging of Neurodegenerative Disease VA Medical Center Principal Investigator: Alzheimer's Disease Neuroimaging Initiative Professor of Medicine, Radiology, Psychiatry, and Neurology University of California, San Francisco, U.S.A. *Advanced MRI to Detect Brain Injury and Neurodegeneration*	

Time	Session	Poster
12:00 – 12:15 PM	**Co-Chair:** **Jordan GRAFMAN** Chief, Cognitive Neuroscience Section National Institute of Neurological Disorders and Stroke *Two Long Term Consequences of Penetrating Head Injuries: Exacerbated Decline and Post-Traumatic Stress Disorder*	
12:20 – 12:50 PM	**Key Note speaker:** **Michael L. COWAN** Chief Medical Officer, BearingPoint Former Surgeon General, U.S. Navy ***Disruptive Innovation in Health Information Technology: the Role of "Search"***	
12:50 – 1:00 PM	Q/A:	
	Scientific Session 13: Spine Instrumentation, Injury, Regeneration and Advancements	POSTER SESSION II 1:00 – 5:00 PM
1:00 – 1:15 PM	**Chair:** **Ross MOQUINE** Associate Professor of Neurosurgery and Orthopedic Surgery, State University of New York, Upstate Medical University *Fused Deposition Models for Three Dimensional Planning of Spinal Deformity Surgery*	
1:15 – 1:30 PM	**Co-Chair:** **Blair CALANCIE** Professor of Neurosurgery, Upstate Medical University, Syracuse *Pulse-train Stimulation for Detecting Medial Malpositioning of Thoracic Pedicle Screws*	
1:30 – 1:45 PM	**Amir VOKSHOOR** Director of MIS, D.I.S.C institute *Spine of the Future*	

1:45 – 2:00 PM	**Kevin CLEARY** Deputy Director Imaging Science & Information System (ISIS) leader scientist of Computer Aided Interventions (CAIMR) group Research Associate Professor, Department of Radiology Lumbardi Comprehensive Cancer Center Georgetown University School of Medicine *Technology and Challenges* *for Minimally Invasive Spine Interventions*	
2:00 – 2:15 PM	**Special Topic** **Ron KIKINIS** Founding Director of Surgical Planning Laboratory Director of The National Center for Image Guided Therapy Professor of Radiology Department of Radiology Brigham & Women's Hospital, Harvard Medical School, Boston, USA *Image Analysis for Conservative Follow-up of meningiomas*	
2:15 – 2 :25 PM	Q/A:	
2:25 – 2 :45 PM	Tea Recess	
	Scientific Session 14: ***Neurophysiology and Functional Neurosurgery***	
2 :45 – 3:00 PM	**Arno VILLRINGER** Professor of Neurology Department of Neurology. Charité Hospital. Humboldt University. Berlin, Germany *Physiology-Empowered* *Functional Brain Imaging*	
3:00 – 3:15 PM	**Co-chair:** **Jeffrey David LEWINE** Executive Director, Alexian Center for Brain Research Executive Director, Illinois Magnetoencephalography Center, Alexian Neurosciences Institute *Multimodal Noninvasive Brain Imaging for guiding* *Neurosurgery: Integration of MEG, fMRI and MR Spectroscopy*	

3:15 – 3:30 PM	**Susan Y. BOOKHEIMER** Associate Professor, Department of Psychiatry and Biobehavioral Sciences, UCLA *fMRI in the Clinic: Presurgical Planning*	
3:30 – 3:45 PM	**Vadim S. ZOTIV** Scientist Los Alamos National Laboratory, Group of Applied Physics *Multi-Channel MRI at Ultra-Low fields Compatible with MEG*	
3:45 – 4:00 PM	**Special Topic** **Igor SAVUKOV** Scientist Princeton University and Los Alamos National Laboratory *Application of atomic magnetometers to MEG and NMR*	
4:00 – 4:10 PM	(Q/A)	
4:10 – 4:30 PM	Coffee Break	
	Scientific Session 15: Brain Injury and Trauma	
4:30 – 4:45 PM	**Chair:** **Deborah WARDEN** National Director, Defense and Veterans Brain Injury Center Walter Reed Army Medical Professor of Neurology and Psychiatry Uniformed Services University of the Health Sciences *Primary Blast Brain Injury-A Case Report*	
4 :45 – 5:00 PM	**Co-Chair:** **Manbir SINGH** Professor of Radiology and Biomedical Engineering University of Southern California *Detection of White-matter Pathways Affected in TBI by DTI-Tractography*	
5:00 – 5:15 PM	**Gregory LEKOVIC** Chief Resident Barrow Neurological Institute *Ethical Issues in NeuroImaging*	

5:00 – 5:15 PM

John R. FORDER Associate Professor of Radiology and Biomedical Engineering Associate Director, Advanced Magnetic Resonance Imaging and Spectroscopy facility *Diffusion imaging at very high fields*	
5:30 – 5:45 PM **Mark S. COHEN** Professor, Departments of Neurology, Radiological Sciences, Psychiatry & Biobehavioral Sciences, and Biomedical Physics at the David Geffen School of Medicine, UCLA; Director, Functionnal MRI Activation Imaging ; Member, Division Of Brain Mapping *Challenges and Opportunities for MRI in Traumatic Brain Injury*	
5:45 – 6:00 PM **Officials** **Closing Remarks** **Farzad MASSOUDI**	

Board of Directors of IBMISPS is proud to Present

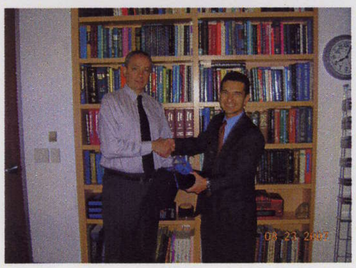
COURAGE AND DEDICATION CRYSTAL AWARD TO:

PIONEER IN MEDICINE TO:

Behnam Badie, MD, FACS

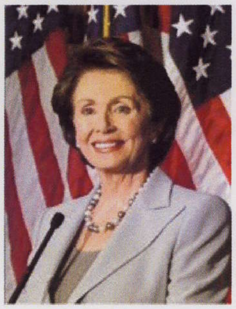
Richard Frakowiack, M.D., Ph.D.

Author W. Toga, Ph.D.

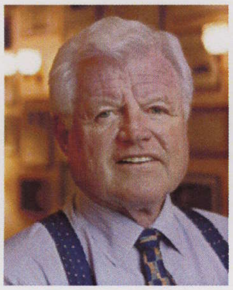


John Mazziotta, MD, Ph.D.

PIONEER IN HEALTHCARE POLICY:



The Honorable Madam Speaker Nancy Pelosi



The Honorable Senator Edward Kennedy

PIONEER IN TECHNOLOGY:

Steve Rusckowski
Executive Vice-President and Chief
Executive Officer Philips Medical Systems

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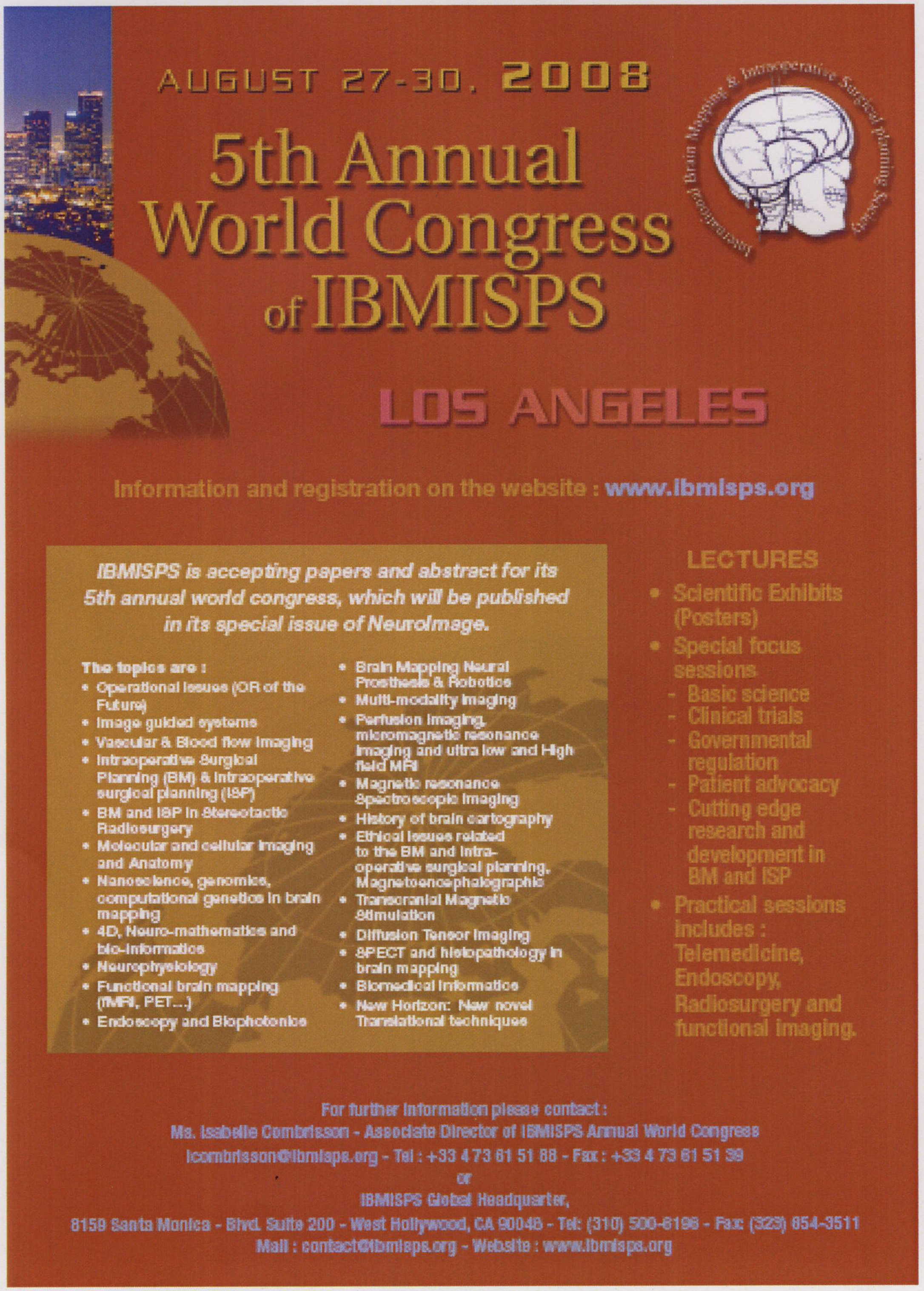
4th Annual World Congress of IBMISPS
September 6 – 8, 2007
Washington USA

We hope to welcome you next year !



Nanoneurosurgery & Image Guided Therapy

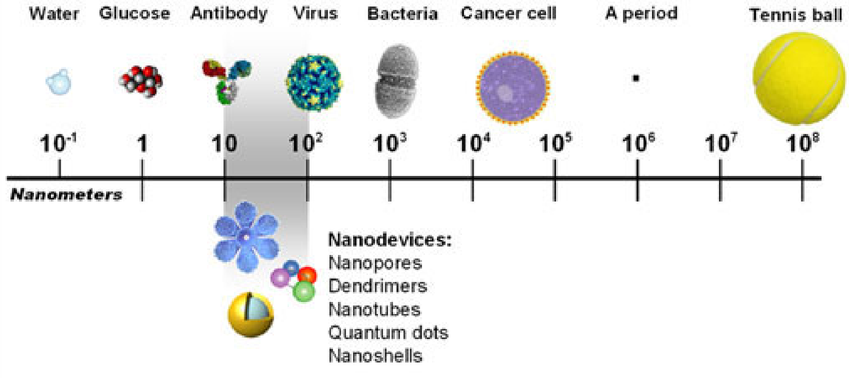
Babak Kateb

September 6, 2007

IBMISPS World Congress

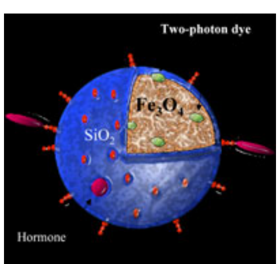
Introduction

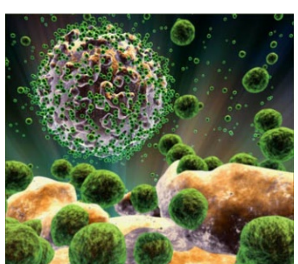
- 130 nanotech drugs/delivery systems in development worldwide[1] [Nature Materials]
- 2004 nanomedicine sales: $6.8 billion
- Approx. $3.8 billion invested in R&D/yr
- Nanomedicine: drug delivery-improved bioavailability
- $65 billion wasted/yr due to low bioavailability
- National Nanotechnology Initiative
- 4 National NIH nanomedicine centers



Nanoparticles

- PEG
- Polystyrene
- PLGA
- Micelles
- Liposomes
- Stem cells
- Bacteria
- Viruses





- Fe nanoparticles: SPIOs
- Gold nanoparticles
- Fullerene nanoparticles
- CNT, MWNCTs
- PFCs
- Quantum dots
- Dendrimers
- Multifunctional nanoparticles

Lipidic Nanoparticles [mulder]

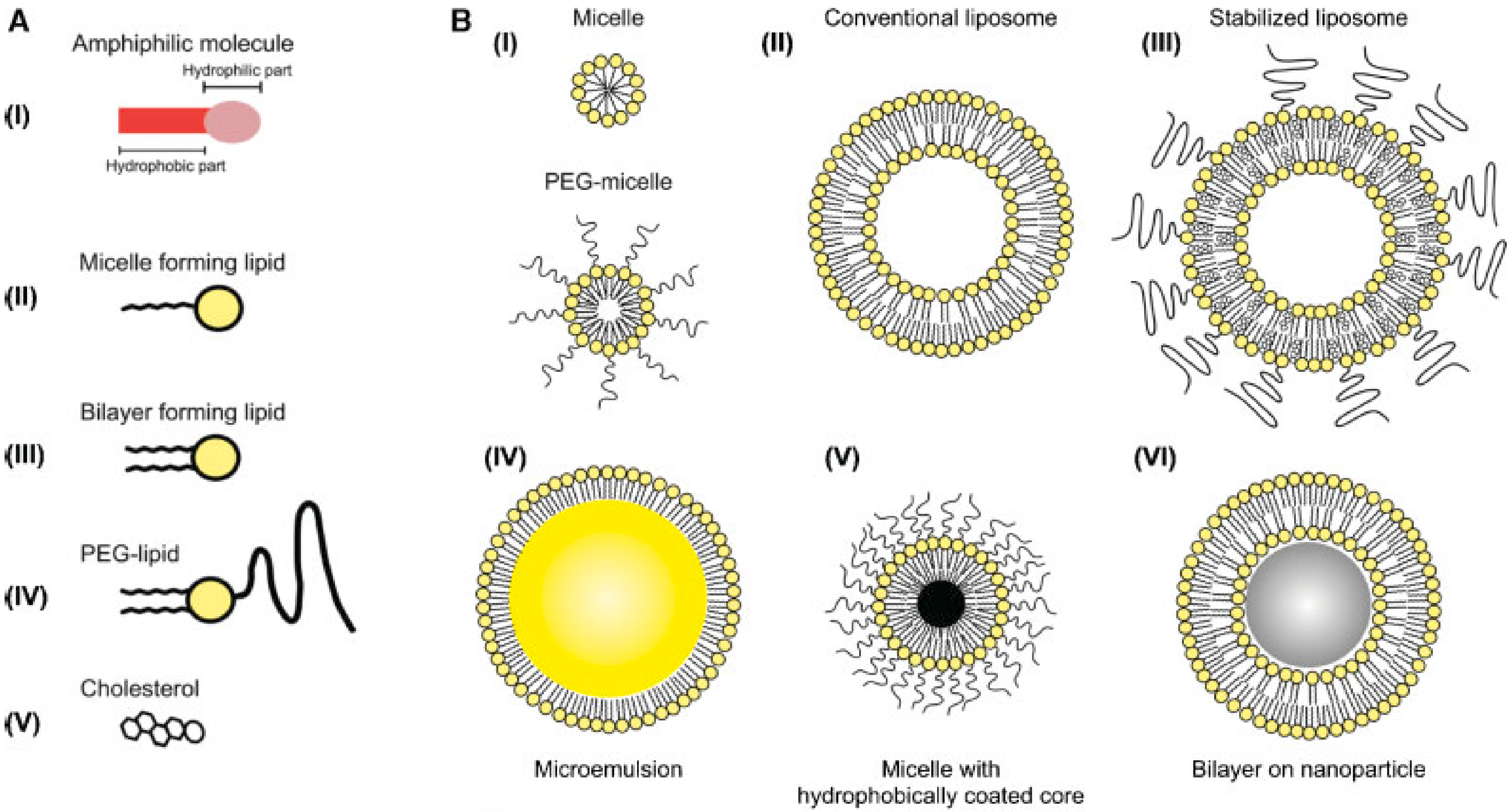
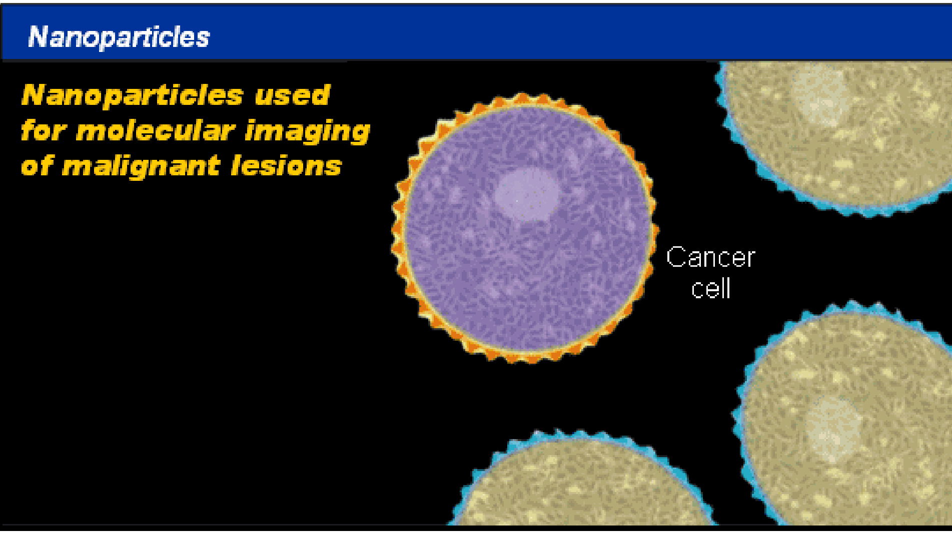
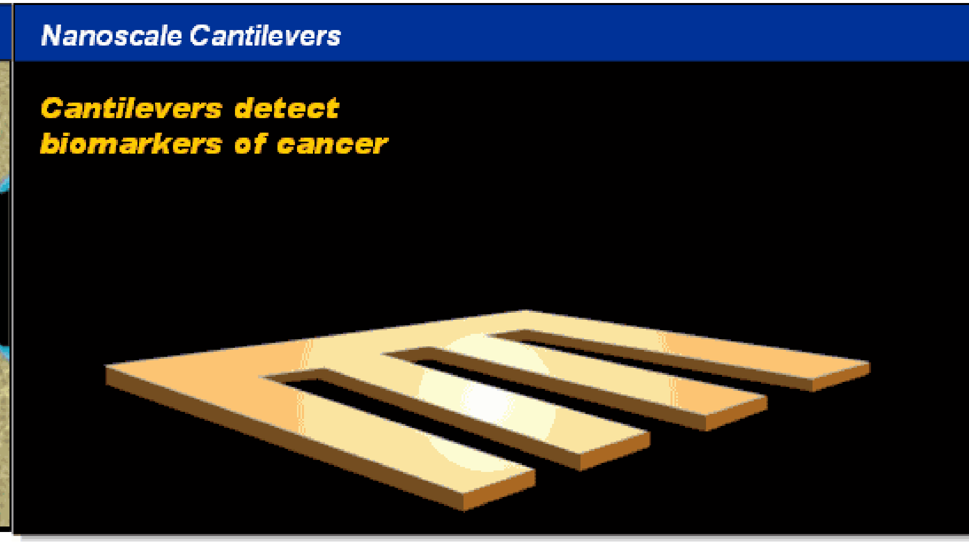


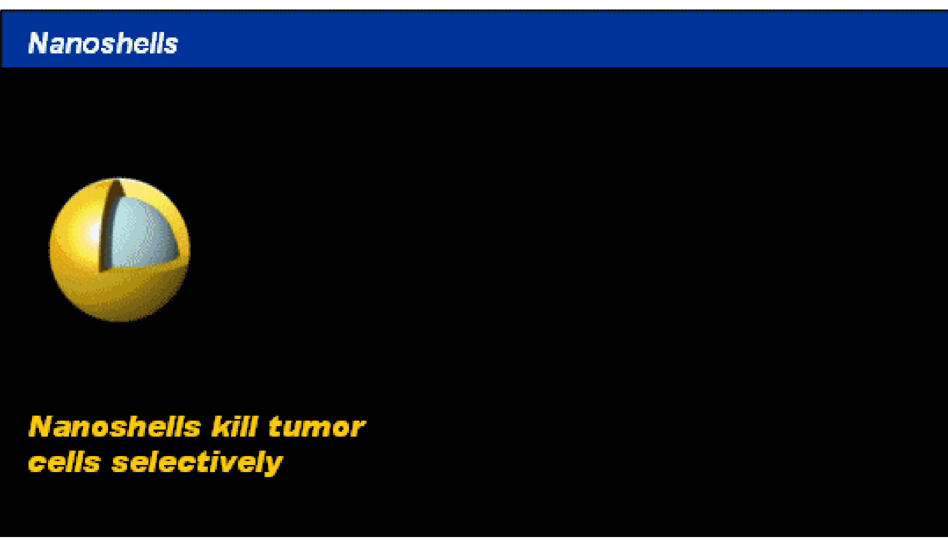
Table 1. Overview of the relaxivities of several different lipidic nanoparticulate MRI contrast agents[a]

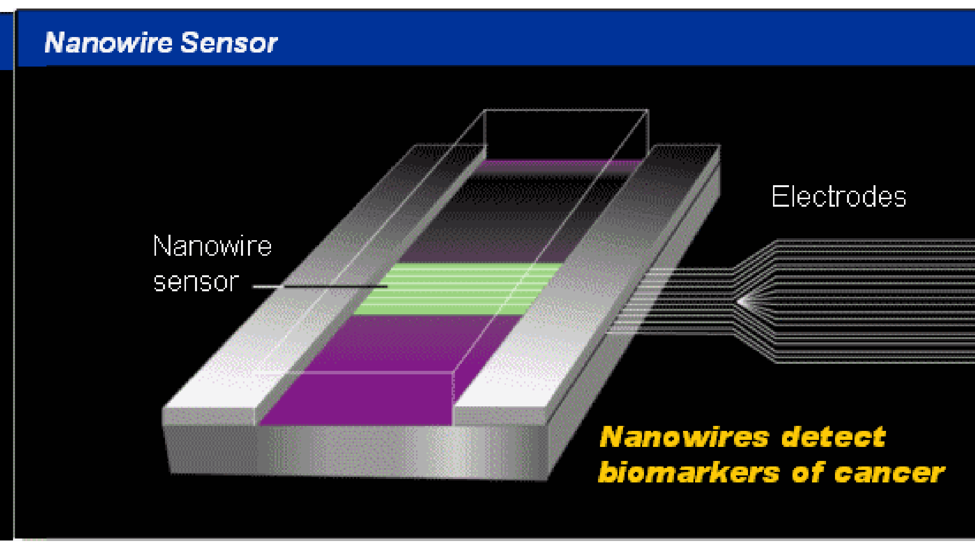
Aggregate type	Reference	Description	Field strength	Temperature (K)	r_1 Gd–DTPA[b]	r_1[b]	r_2[b]
Liposomes	Tilcock *et al.* (112)	Gd–DTPA in lumen liposomes 400 nm	1.5 T		2.79	0.42	
		Gd–DTPA in lumen liposomes 70 nm	1.5 T		2.79	1.60	
	Kim *et al.* (130)	MHE–DTTA in bilayer liposomes	0.47 T		4.1	31.9	
		BME–DTTA in bilayer liposomes	0.47 T		4.1	27.1	
	Tilcock *et al.* (132)	Stearyl ester–DTPA–Gd in bilayer liposomes	20 MHz[c]	308		23	
		Stearylamide–DTPA–Gd in bilayer liposomes	20 MHz[c]	308		13	
	Storrs *et al.* (30)	Polymerized liposomes long spacer	2.0 T		4.24	12.2	
		Polymerized liposomes short spacer	2.0 T		4.24	5.7	
	Glogard *et al.* (34)	Amphiphilic Gd chelates in bilayer	20 MHz[c]	300	4[d]	47	
		Amphiphilic Gd chelates in bilayer	60 MHz[c]	300	4.5[d]	25	
	Bulte and De Cuyper (40)	Magnetoliposomes	1.5 T	310		3	210
		Stealth magnetoliposomes	1.5 T	310		3	240
	Bertini *et al.* (137)	Paramagnetic liposomes	20 MHz[c]	298	4[d]	12	
		Paramagnetic liposomes	60 MHz[c]	298	4.5[d]	12.5	
	Strijkers *et al.* (149)	Gd–DTPA–BSA-containing liposomes	20 MHz	310	3.8	8.2	
Micelles	Nicolle *et al.* (193)	Gadofluorine	20 MHz[c]	298	4[d]	22	
		Gadofluorine	60 MHz[c]	298	4.5[d]	12	
	Hovland *et al.* (135)	Amphiphilic GdPCTA-[12]	20 MHz[c]	298	4[d]	26	
			60 MHz[c]	298	4.5[d]	28	
	Accardo *et al.* (156)	Mixed micellar aggregates	20 MHz[c]	298	4[d]	18	
			60 MHz[c]	298	4.5[d]	18	
	Mulder and van Tilborg	Micellular iron oxide MCIO (unpublished data)	20 MHz[c]	298	4[d]	15	200
Microemulsion	Winter *et al.* (194)	Nanoparticles Gd–DTPA–BOA	1.5 T	313	4.5[d]	17.7	25.3
		Nanoparticles Gd–DTPA–PE	1.5 T	313	4.5[d]	33.7	50
High-density lipoprotein	Frias *et al.* (102)	HDL-like nanoparticles	65 MHz	298	4.5[d]	10.4	

[a]Note that the ionic relaxivity is given. The relaxivity per particle is much higher, since the particles depicted in the table carry high payloads of Gd or Fe.
[b]r_1 Gd–DTPA: T_1 relaxivity of Gd–DTPA expressed in $mM^{-1}s^{-1}$. r_1: T_1 relaxivity of the contrast agent referred to expressed in $mM^{-1}s^{-1}$. r_2: T_2 relaxivity of the contrast agent referred to expressed in $mM^{-1}s^{-1}$.
[c]NMRD profile was given in the reference.
[d]Data from Aime *et al.* (3).

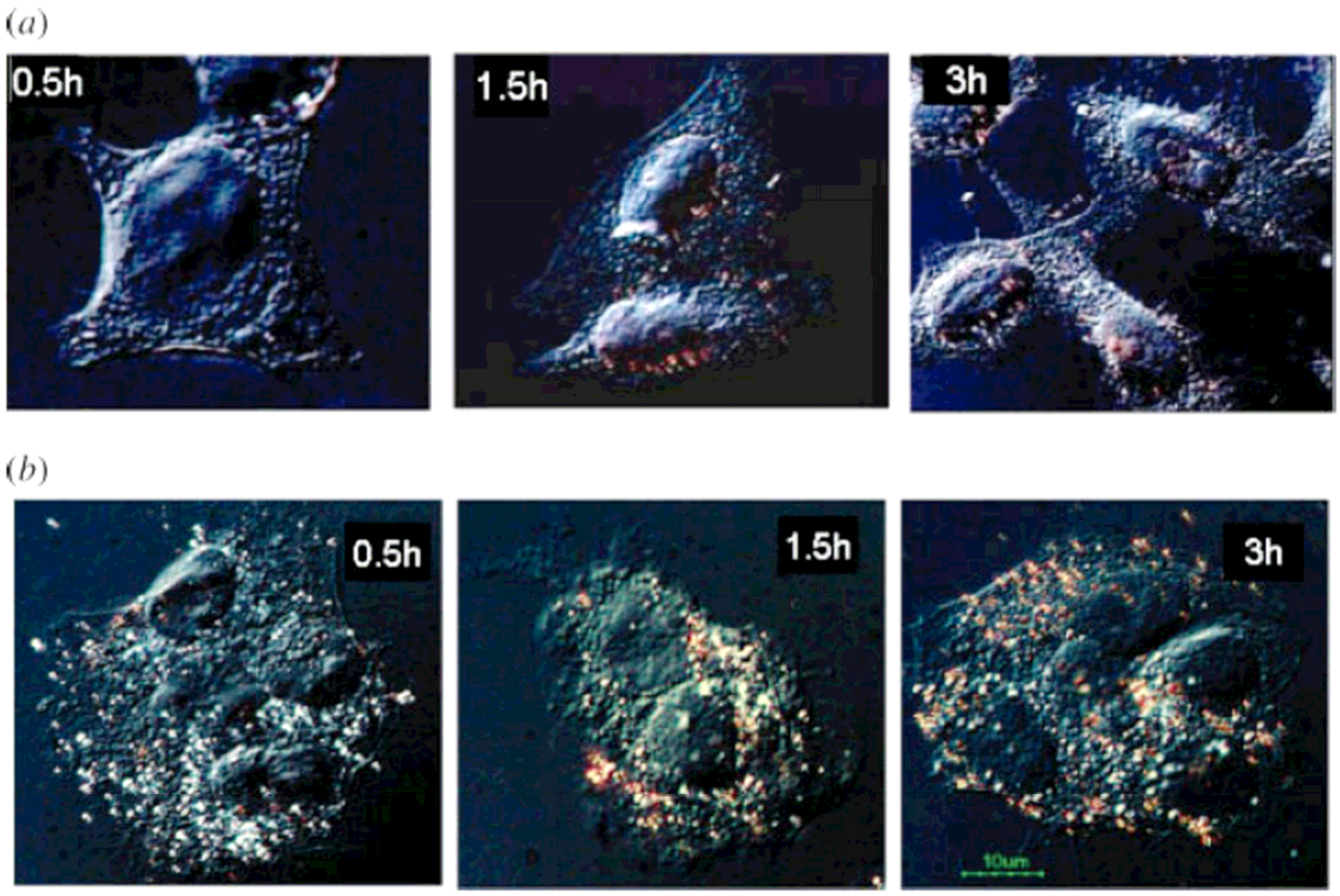

Nanoparticles
Nanoparticles used for molecular imaging of malignant lesions
Cancer cell


Nanoscale Cantilevers
Cantilevers detect biomarkers of cancer


Nanoshells
Nanoshells kill tumor cells selectively


Nanowire Sensor
Electrodes
Nanowire sensor
Nanowires detect biomarkers of cancer

Gold Nanoparticles [Liu]



Nanoneurosurgery

- Ability to image, model, track lesions
- Earlier diagnosis
- Therapy: thermal ablation2*, target tumor angiogenesis, nanochemotherapy, nano-drug delivery systems, real time delivery to brain parenchyma[2]
- Follow-up: monitor treatment

FE-Pro: ferrumoxide-protamine sulfate (SPIO)

- FE-Pro manufactured by Feridex, FDA approved for Hepatic use
- Need for FDA Approval for Clinical Application of FE-Pro in Neurosurgery
- MRI & SPIOs [Rad, Arbab et al]

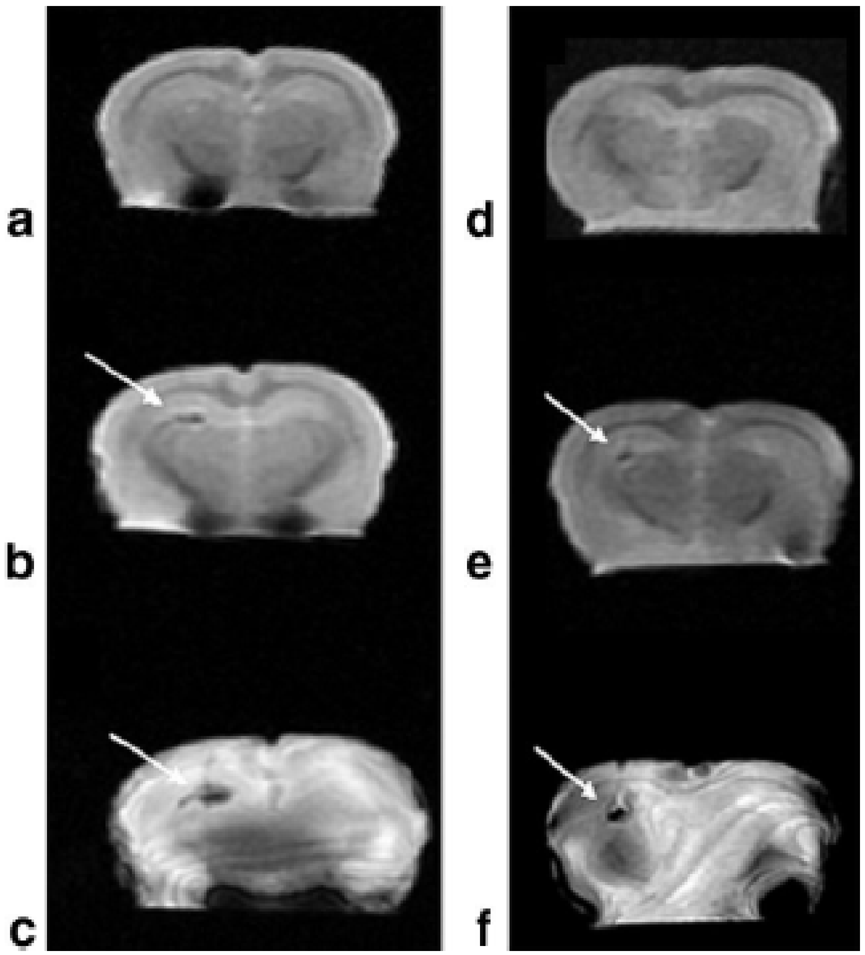
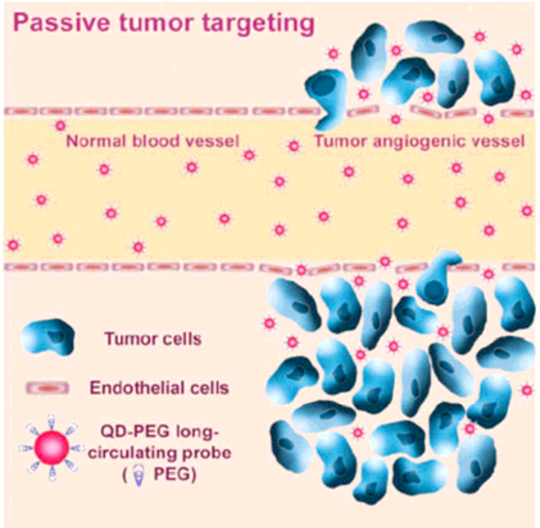
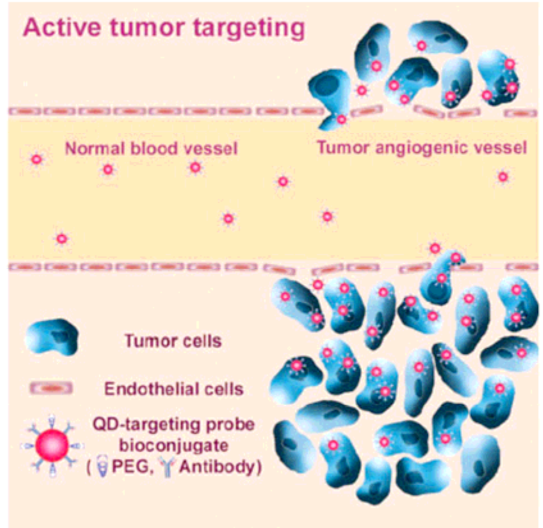
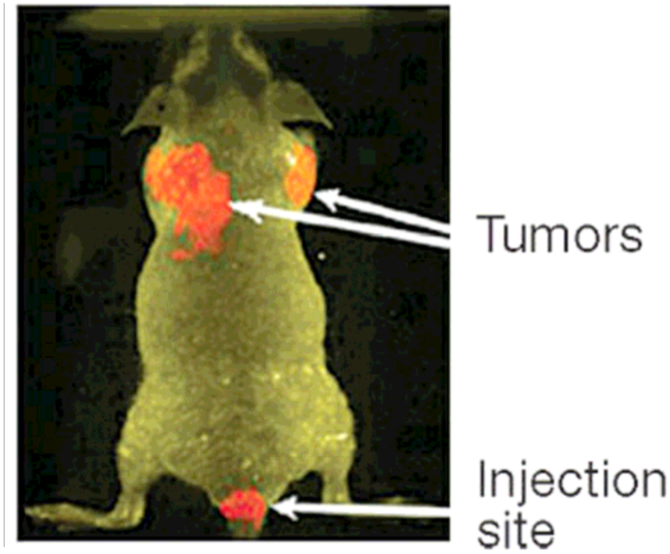


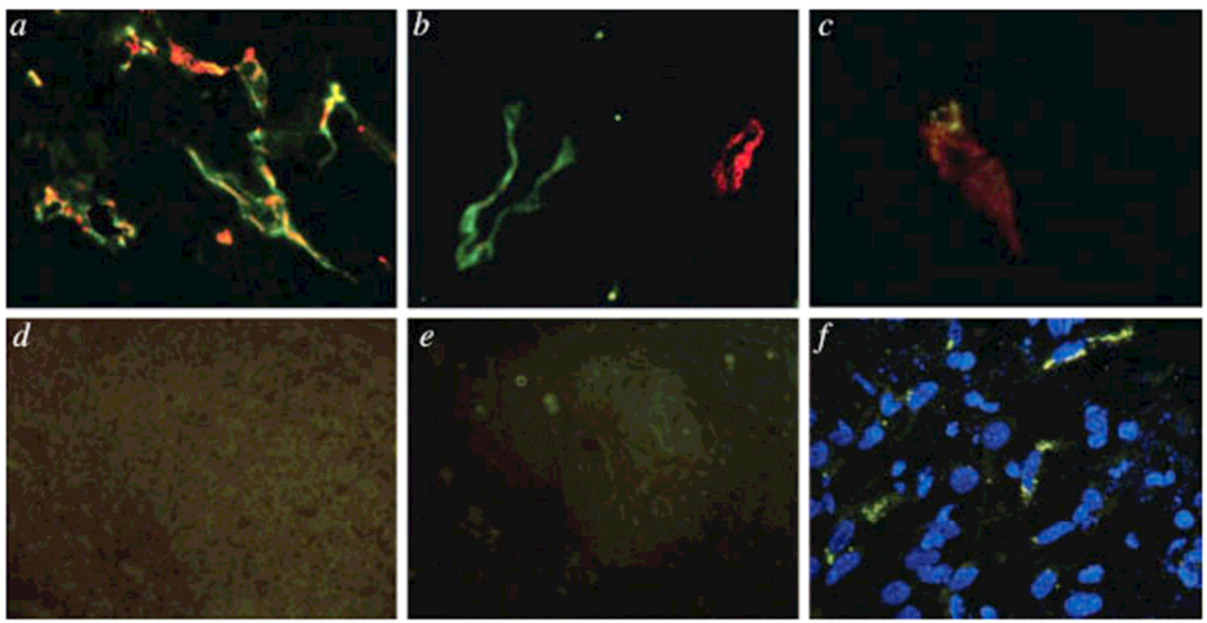
Image Guided Therapy in Oncology

- Simultaneous Molecular imaging cell diagnostic & selective photothermal therapy
- Nanoprobes for detection of neuroblastoma: MR and fluorescence
- Tumor targeting [liu et al], Tumor Angiogenesis
- Clean margins
- Fe oxide nanocrystals: for liver mets, metastatic lymph nodes, inflammation, degenerative disease


Passive tumor targeting
Normal blood vessel
Tumor angiogenic vessel
Tumor cells
Endothelial cells
QD-PEG long-circulating probe
(PEG)


Active tumor targeting
Normal blood vessel
Tumor angiogenic vessel
Tumor cells
Endothelial cells
QD-targeting probe bioconjugate
(PEG, Antibody)


Tumors
Injection site

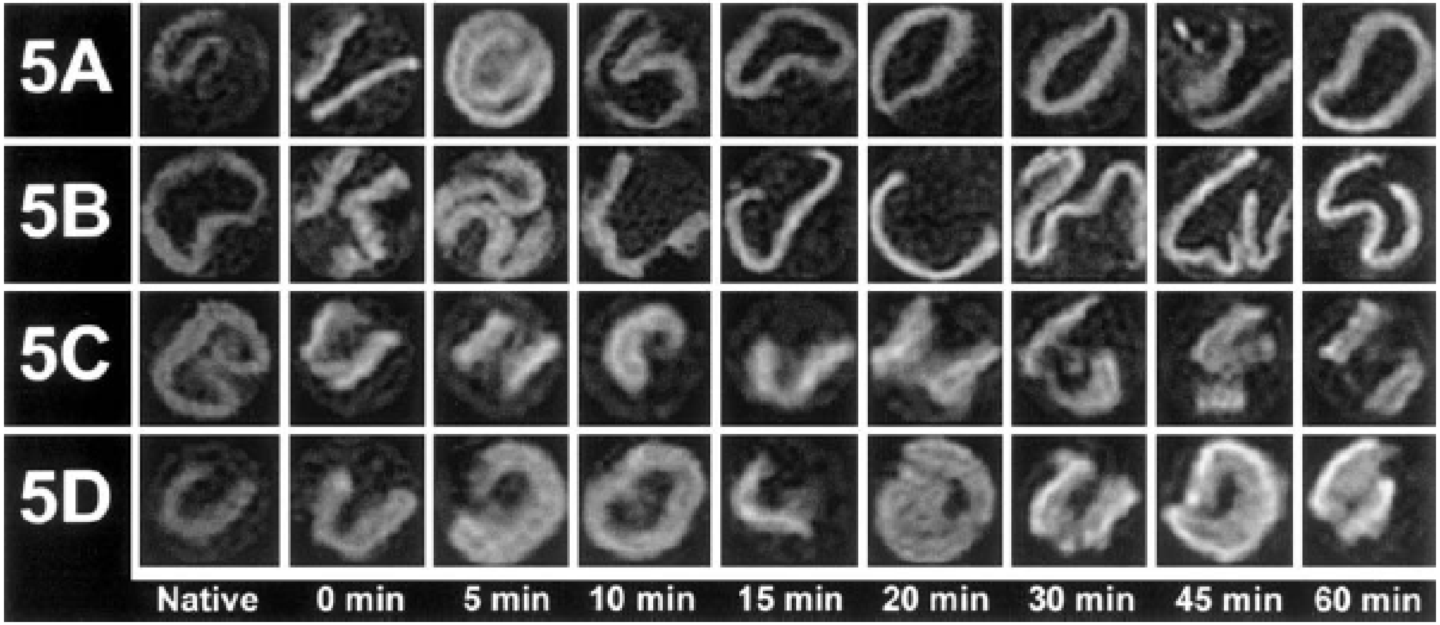

a
b
c
d
e
f

Sentinel Lymph Node Mapping

- MR lymphangiography
- Lymph node staging vs. sampling
- Targeted therapy of sentinel nodes
- Intraoperative lymph node mapping[3]

Detection of Cardiovascular lesions

- Thrombosis 4*
- Atherosclerosis: detection of subclinical atherosclerosis4, real-time imaging, pharmacotherapy, intervention
- Improve MR imaging of atherosclerotic lesions
- Detection of increased intimal thickening via contrast enhanced MR with paramagnetic liposomes [mulder]
- New agents for MR Angiography



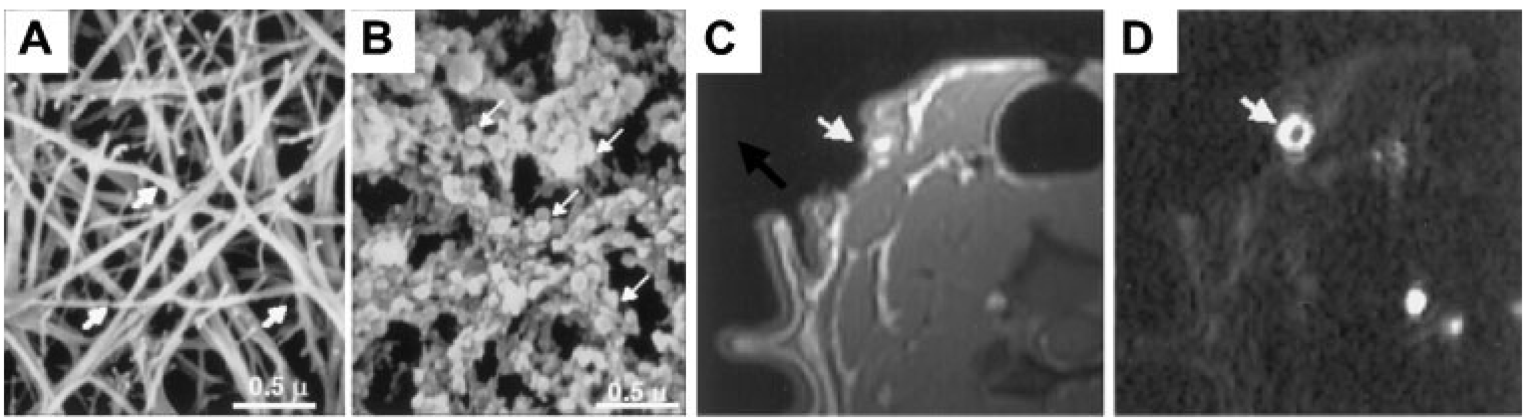


Figure 8. Scanning electron micrographs of control fibrin clot (A) and fibrin-targeted paramagnetic nanoparticles bound to clot surface (B). Arrows indicate (A) fibrin fibril and (B) fibrin-specific nanoparticle-bound fibrin epitopes. Thrombus in external jugular vein targeted with fibrin-specific paramagnetic nanoparticles demonstrating dramatic T_1-weighted contrast enhancement in gradient-echo image (C) with flow deficit (arrow) of thrombus in corresponding phase-contrast image (D). Adapted from Figs 1 and 5 of Flacke *et al.*, Novel MRI contrast agent for molecular imaging of fibrin: implications for detecting vulnerable plaques. *Circulation* 2001; **104**: 1280–1285, with permission from Lippincott Williams & Wilkins

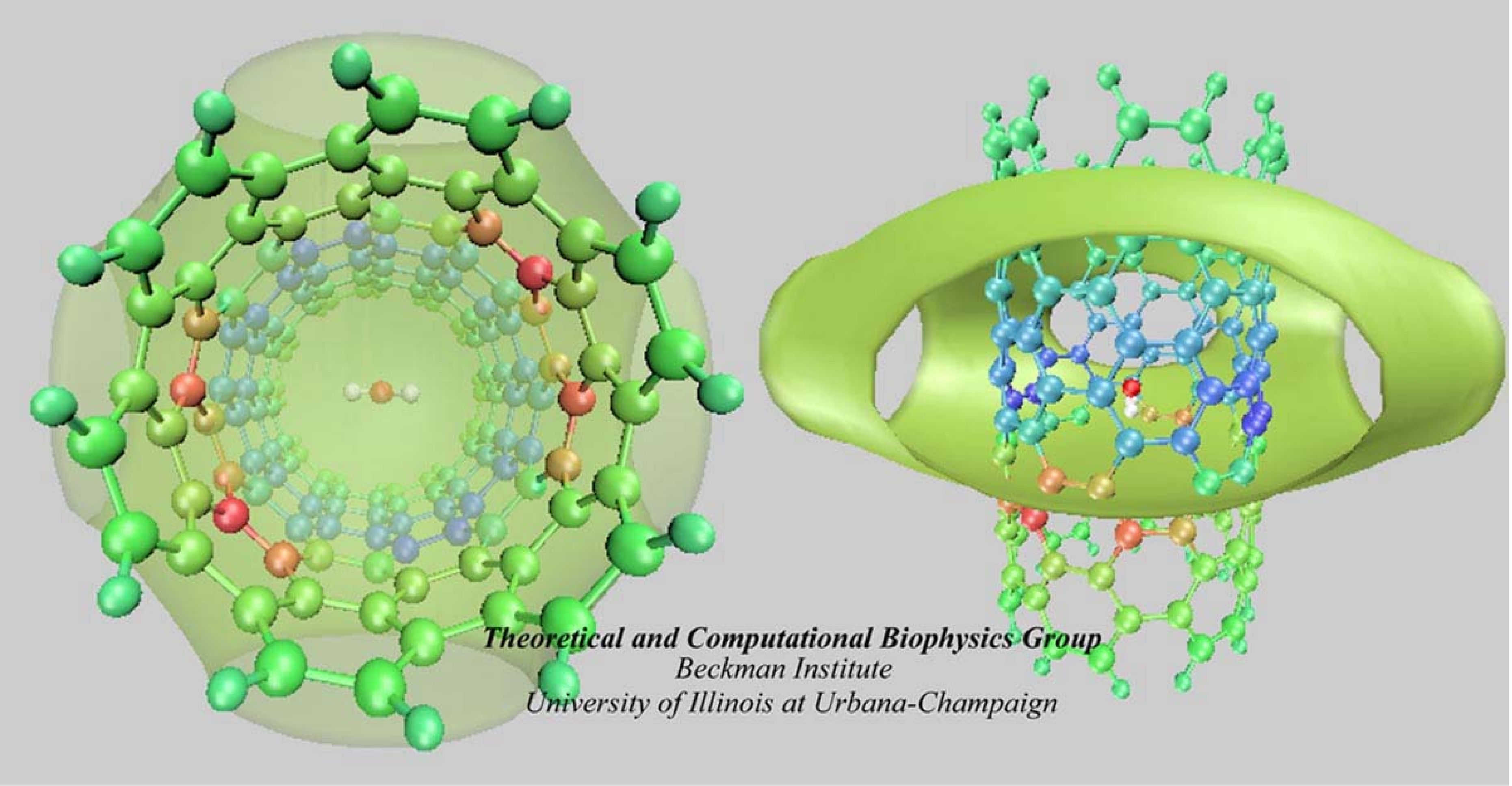
Drug Delivery

- Local reversible disruption of the blood brain barrier with ultrasound bursts[5]
- Lysolipid based temperature sensitive liposomes with chemotherapy drugs, local thermal treatment➔improve efficacy of treatment[6]
- Personalized targeted gene therapy

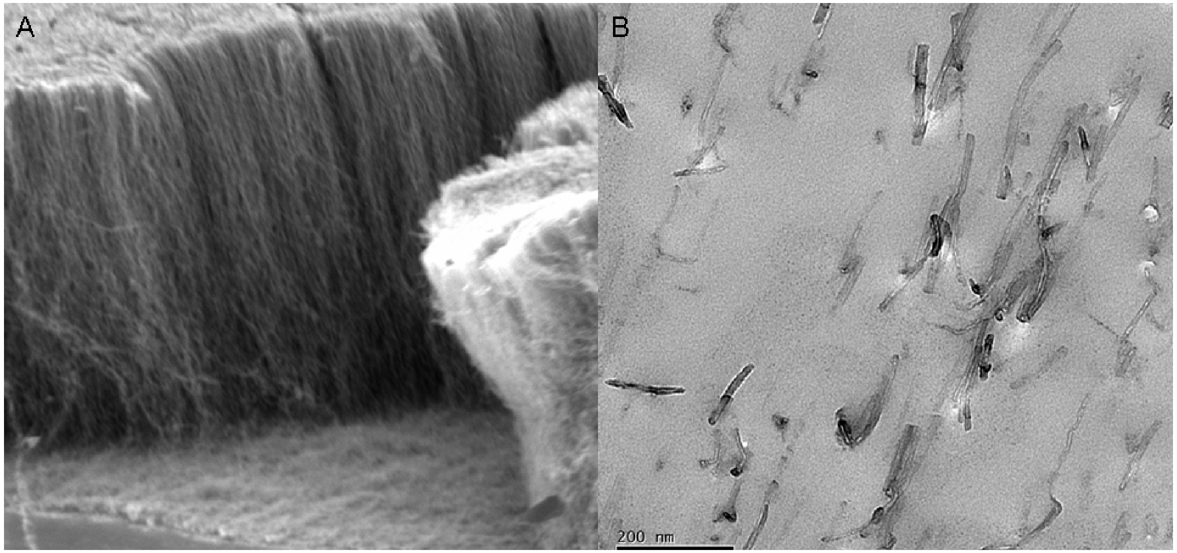
Table 1
Nanoscale drug delivery technologies

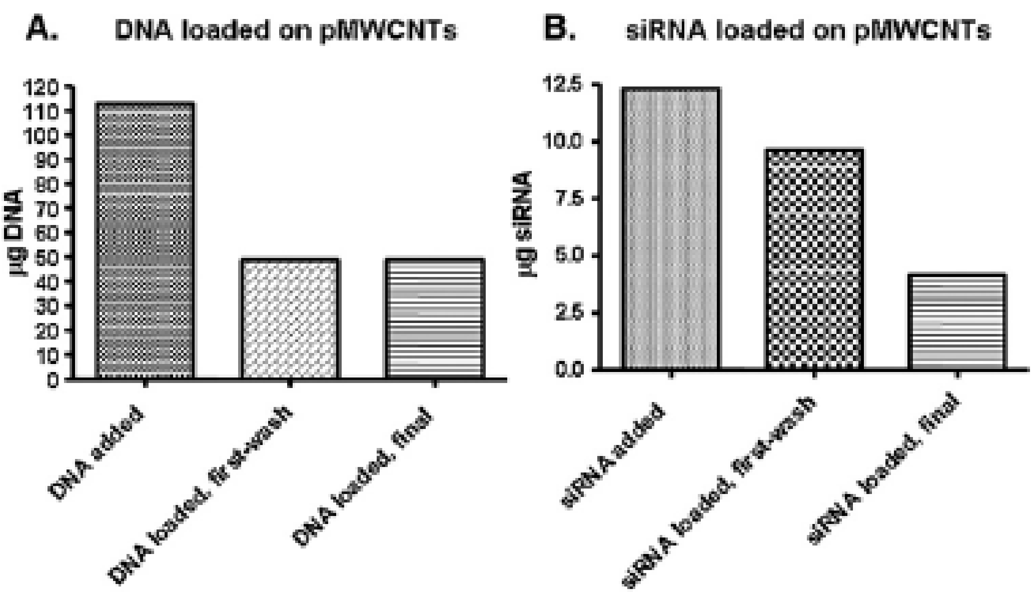
Drug delivery technology	Materials	Nanostructure forms
Biologic	Lipids	Vesicles, nanotubes, rings;
	Peptides	Nanoparticles
	Nucleic acids	
	Polysaccharides	
	Viruses	
Polymeric	Poly(lactic acid)	Vesicles, spheres, nanoparticles
	Poly(glycolic acid)	Micelles, dendrimers
	Poly(alkylcyanoacrylate)	
	Poly(3-hydroxybutanoic acid)	
	Poly(organophosphazene)	
	Poly(ethylene glycol)	
	Poly(caprolactone)	
	Poly(ethylene oxide)	
	Poly(amidoamine)	
	Poly(L-glutamic acid)	
	Poly(ethyleneimine)	
	Poly(propylene imine)	
Silicon based	Silicon	Porous, nanoparticles
	Silicon dioxide	Nanoneedles
Carbon based	Carbon	Nanotubes, fullerness
Metallic	Gold	Nanoparticles, nanoshells
	Silver	
	Palladium	
	Platinum	

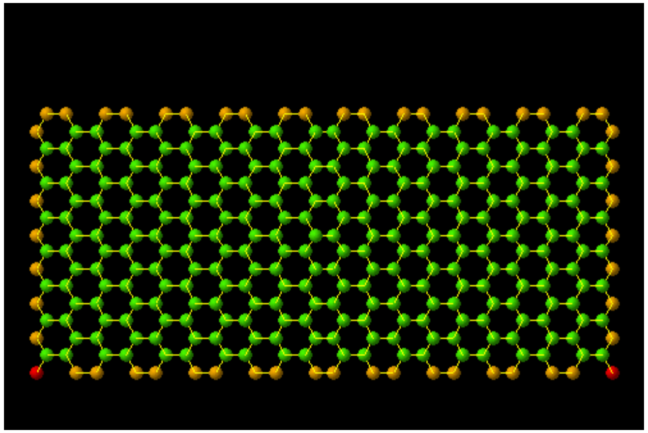
Carbon Nanotubes

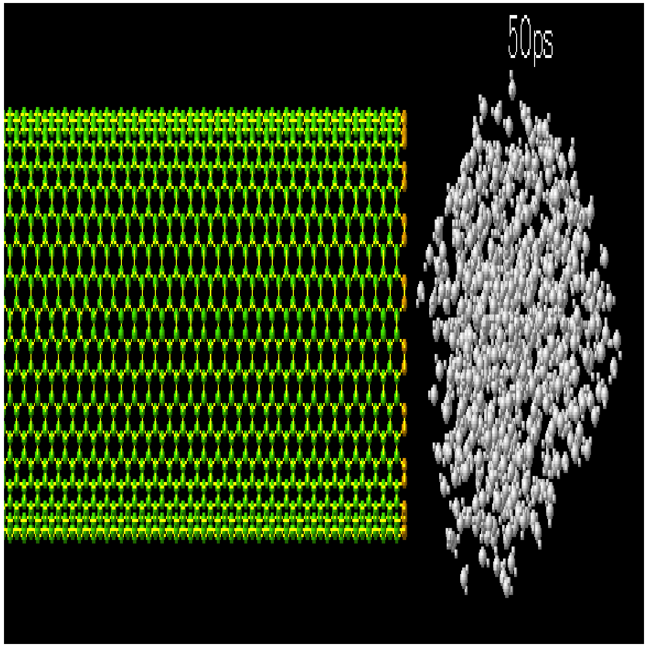


Loading of pMWCNTs[7]

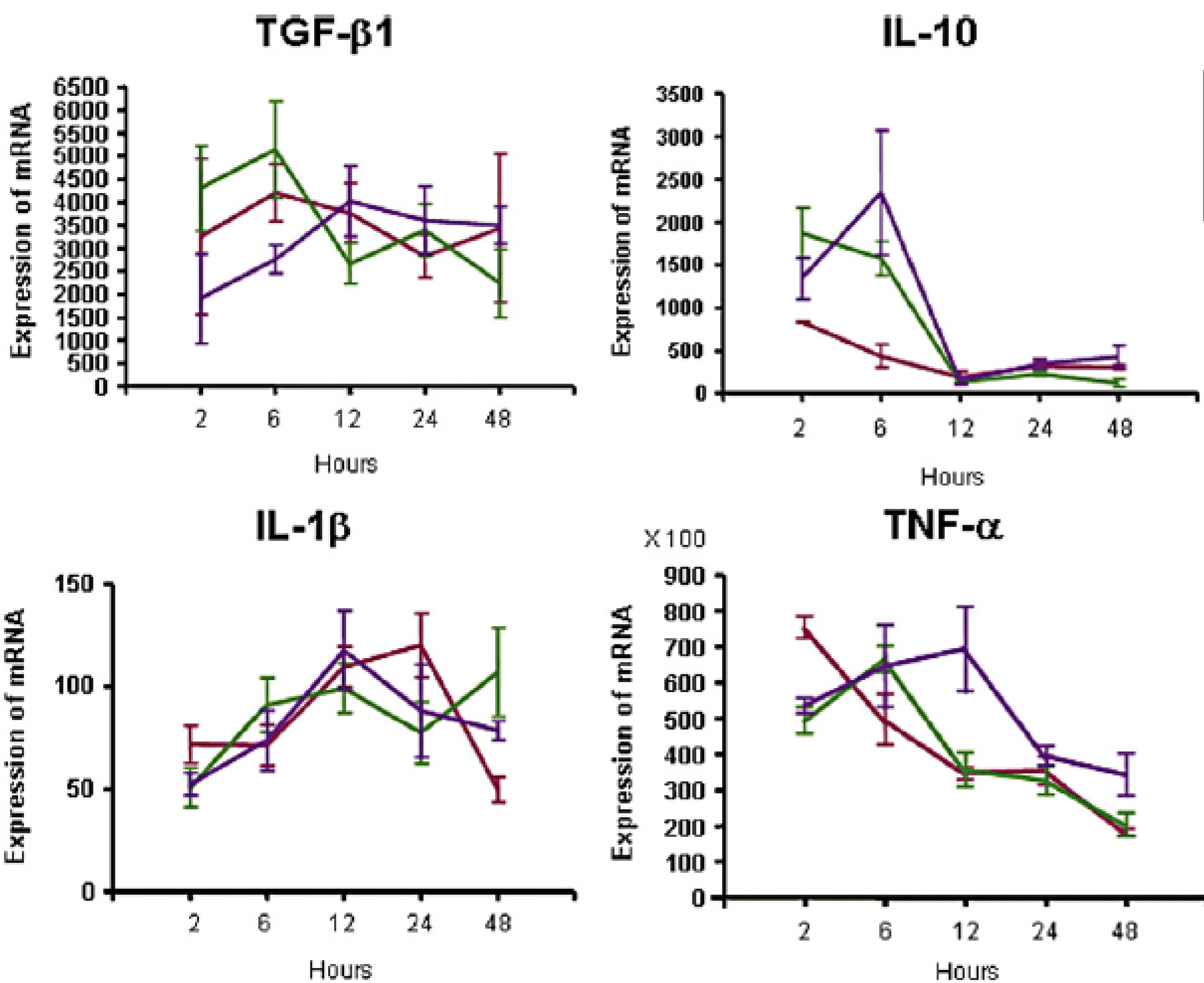


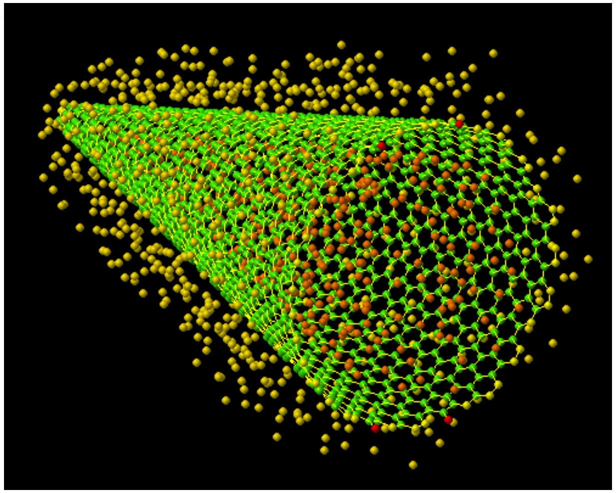




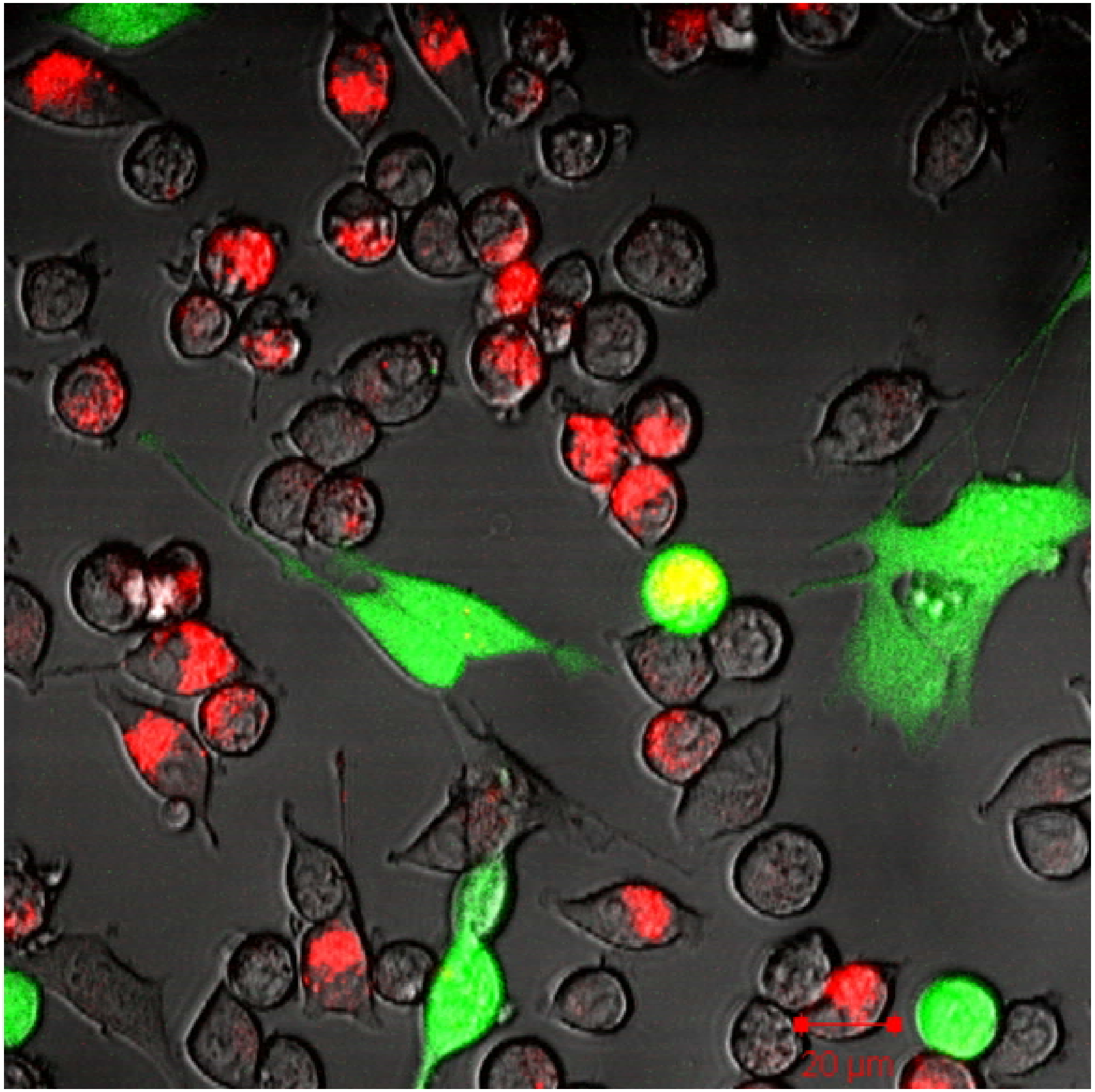


Cytokine Expression Profile for BV2 with and without MWCNT

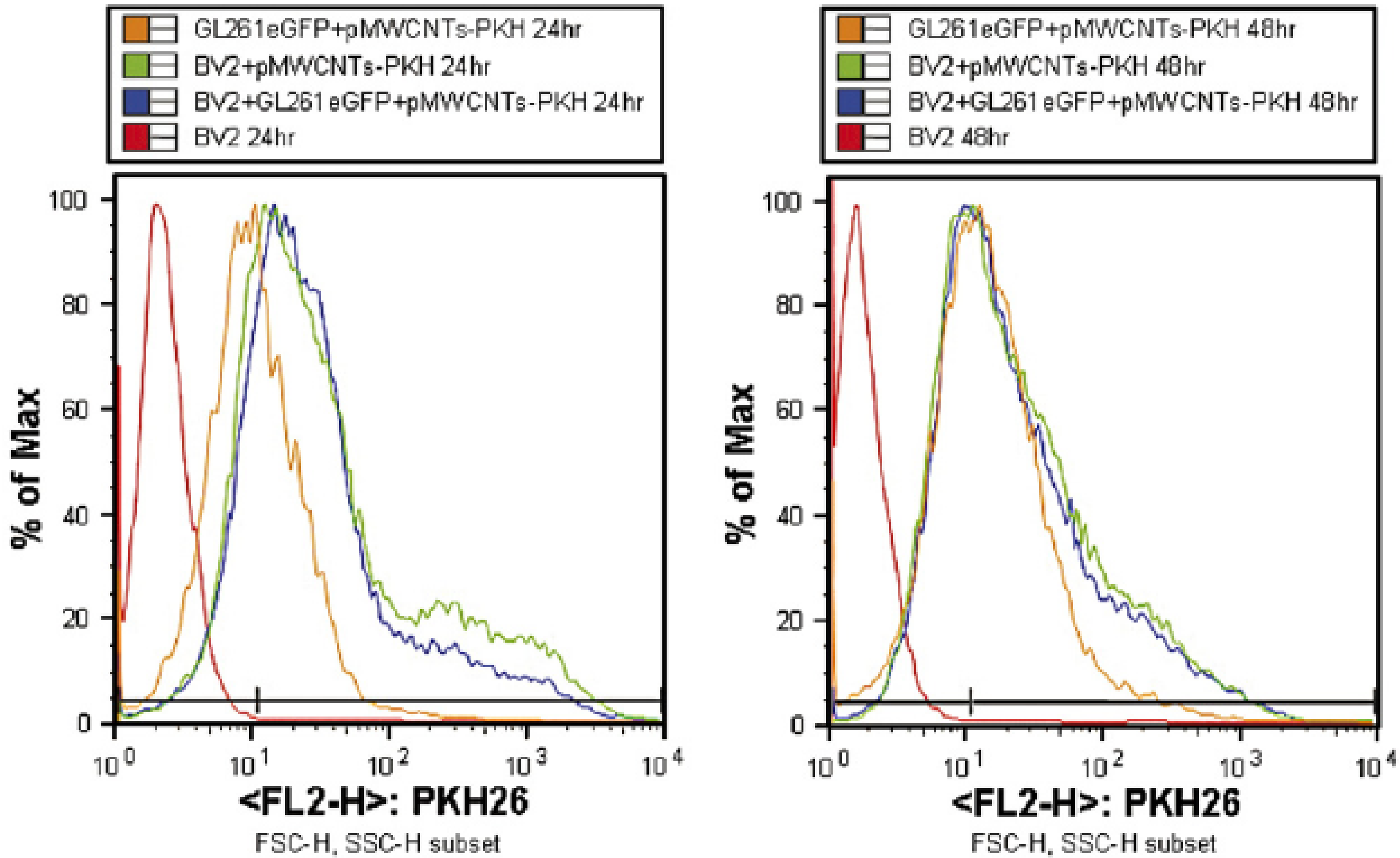




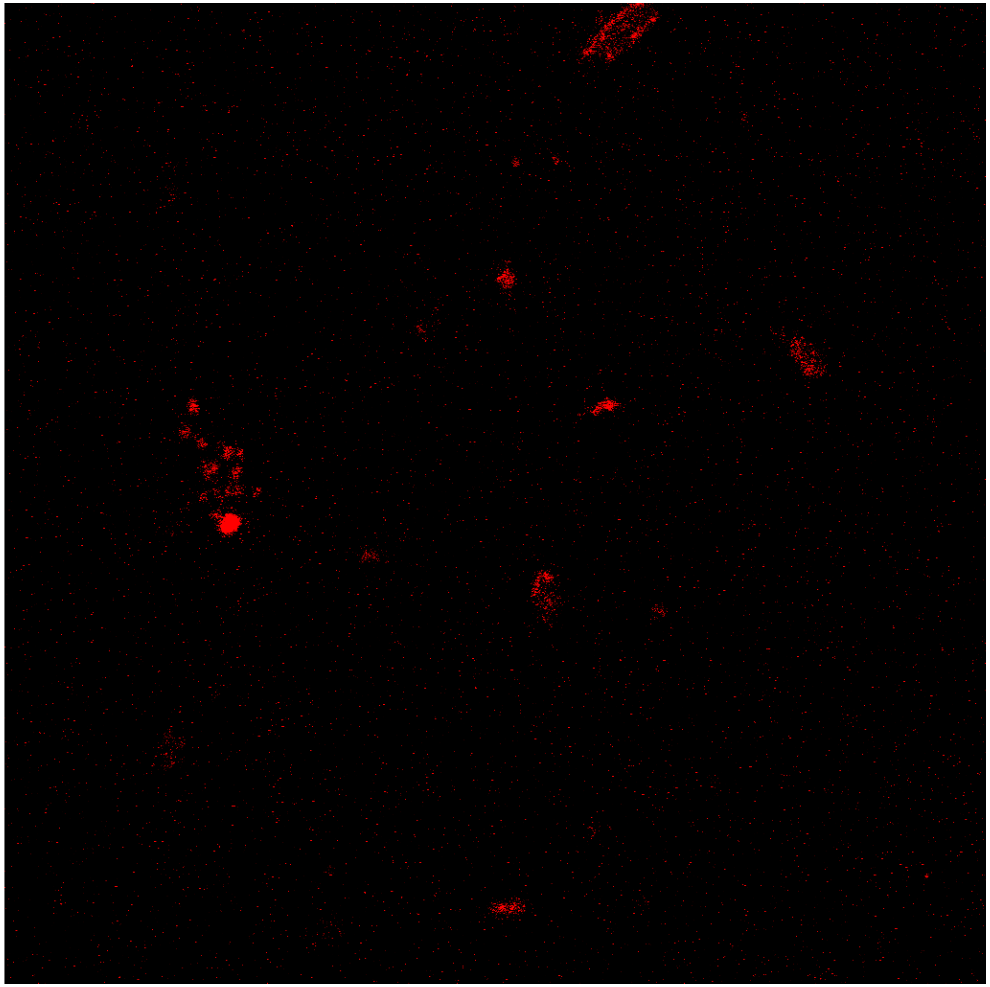
MWCNT: Image Guided Therapy



Preferential Internalization of pMWCNTs in GL261eGFP and BV2 cell lines



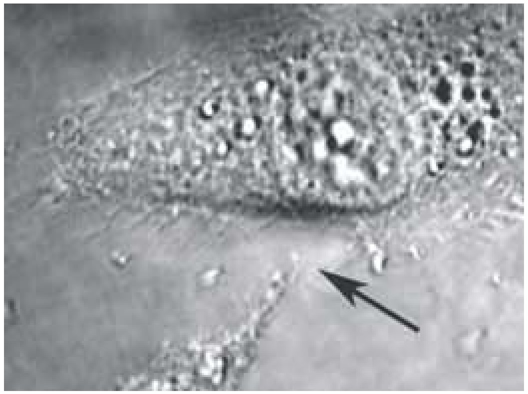
Internalization of MWCNTs in Macrophages

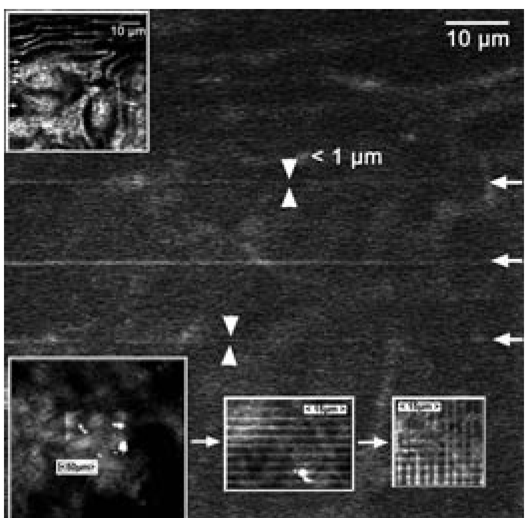


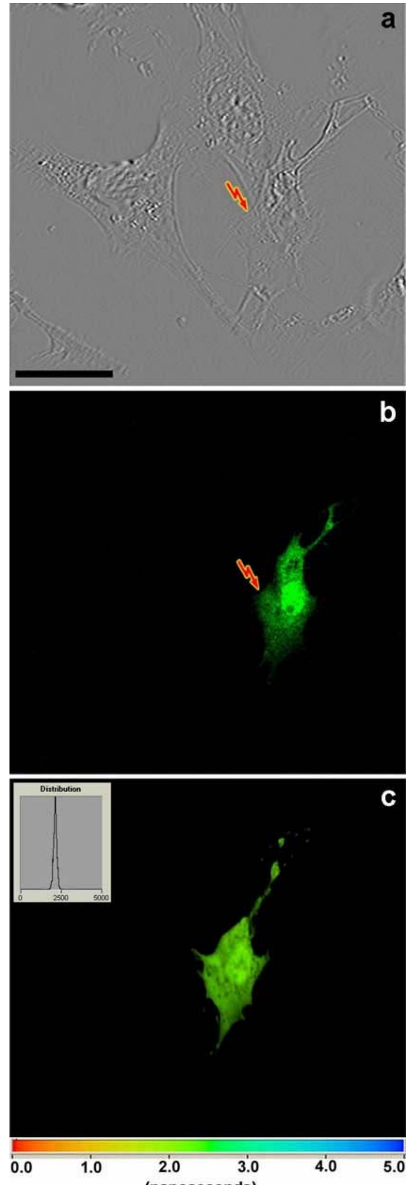
Nanosurgery: femtosecond laser surgery, dx,target-retina

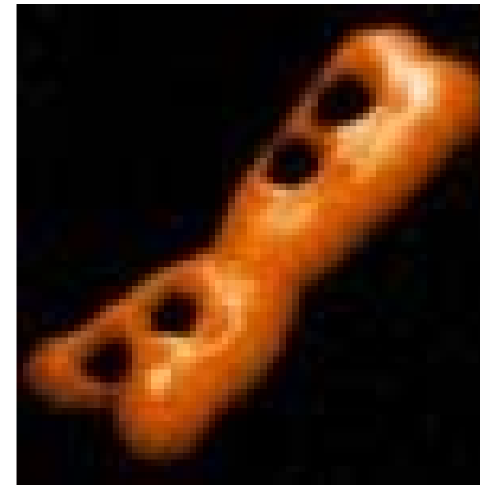
- Optical bx
- dissection of human chromosomes
  intracellular and intratissue nanosurgery
  world-smallest cut size (85 nm)

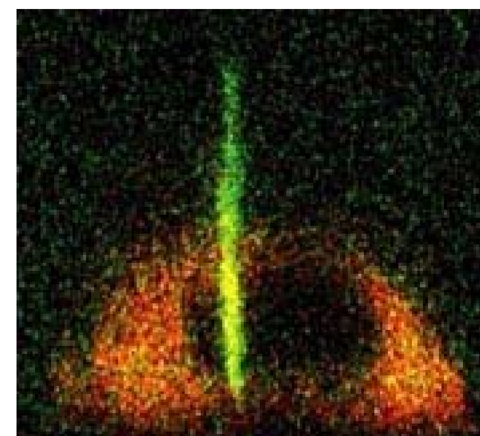
Femtosecond Laser Nanosurgery



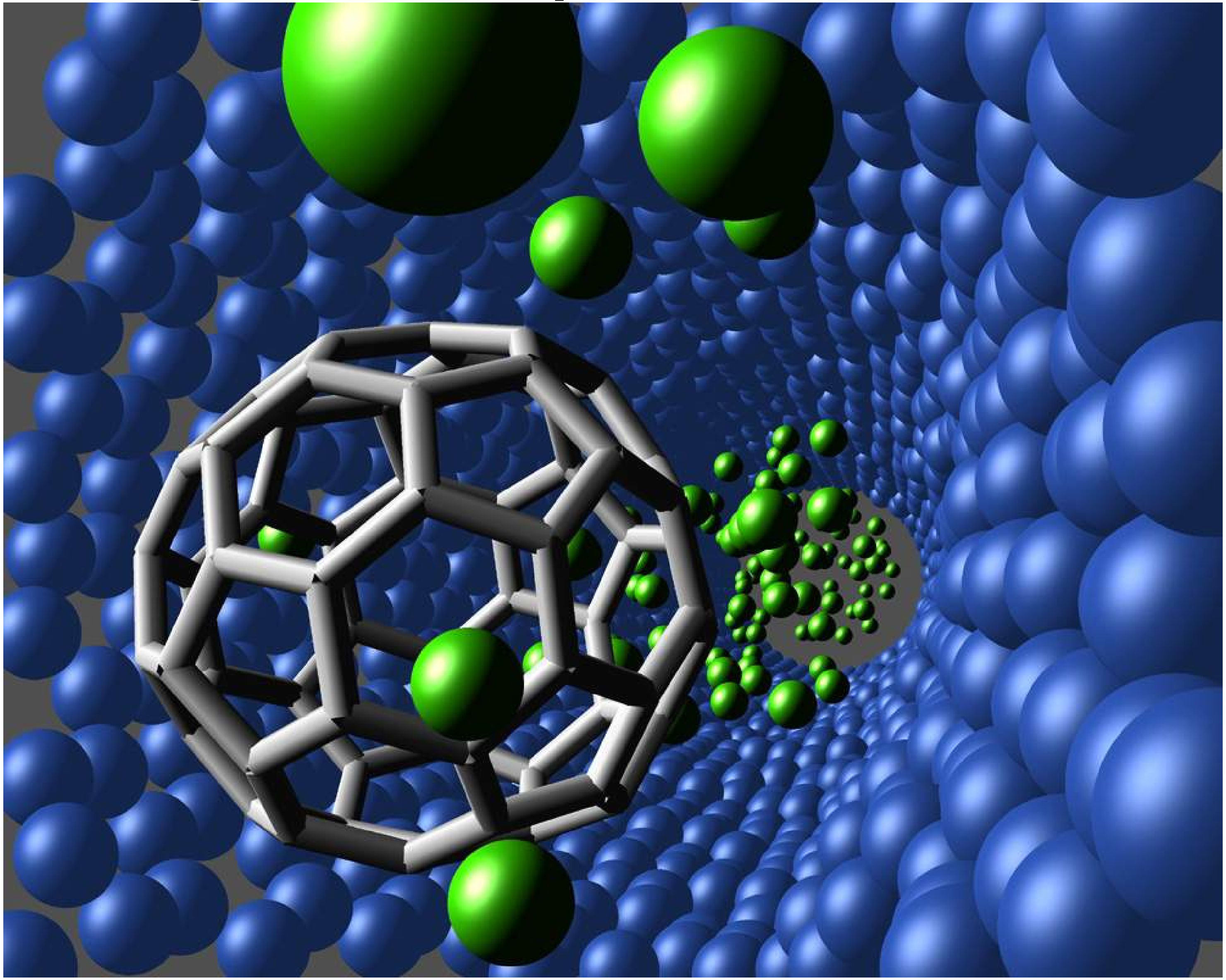




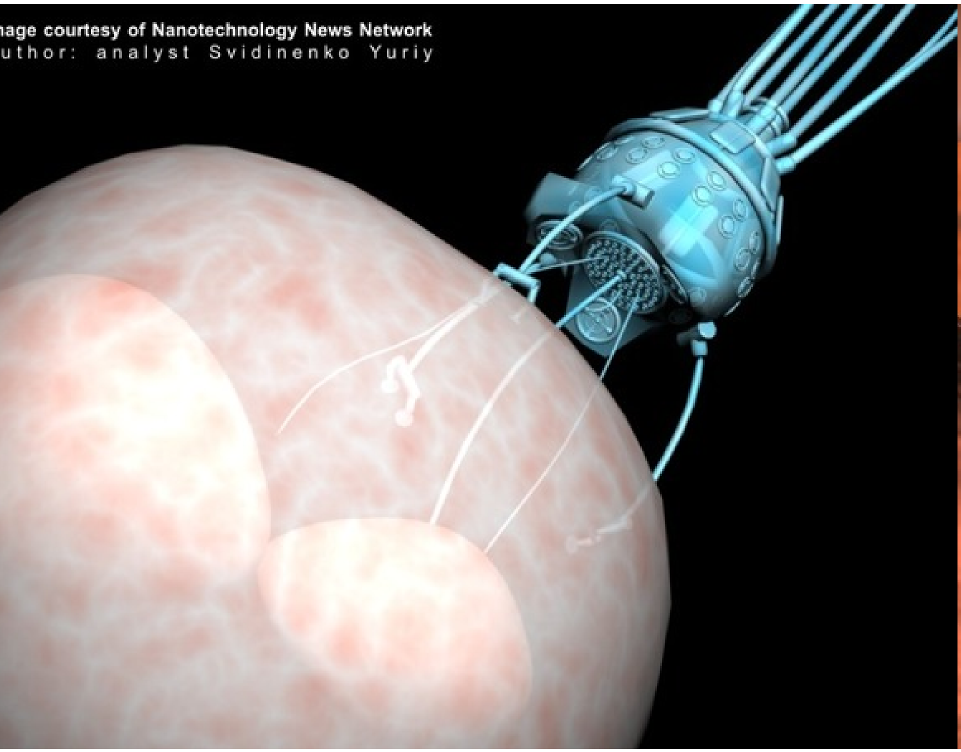


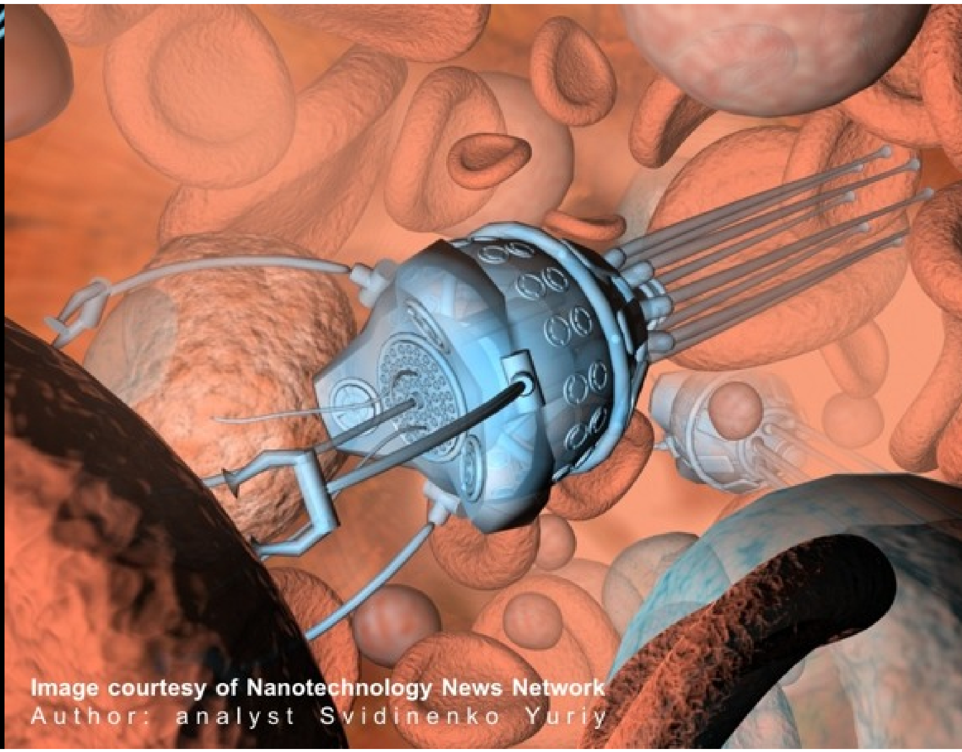


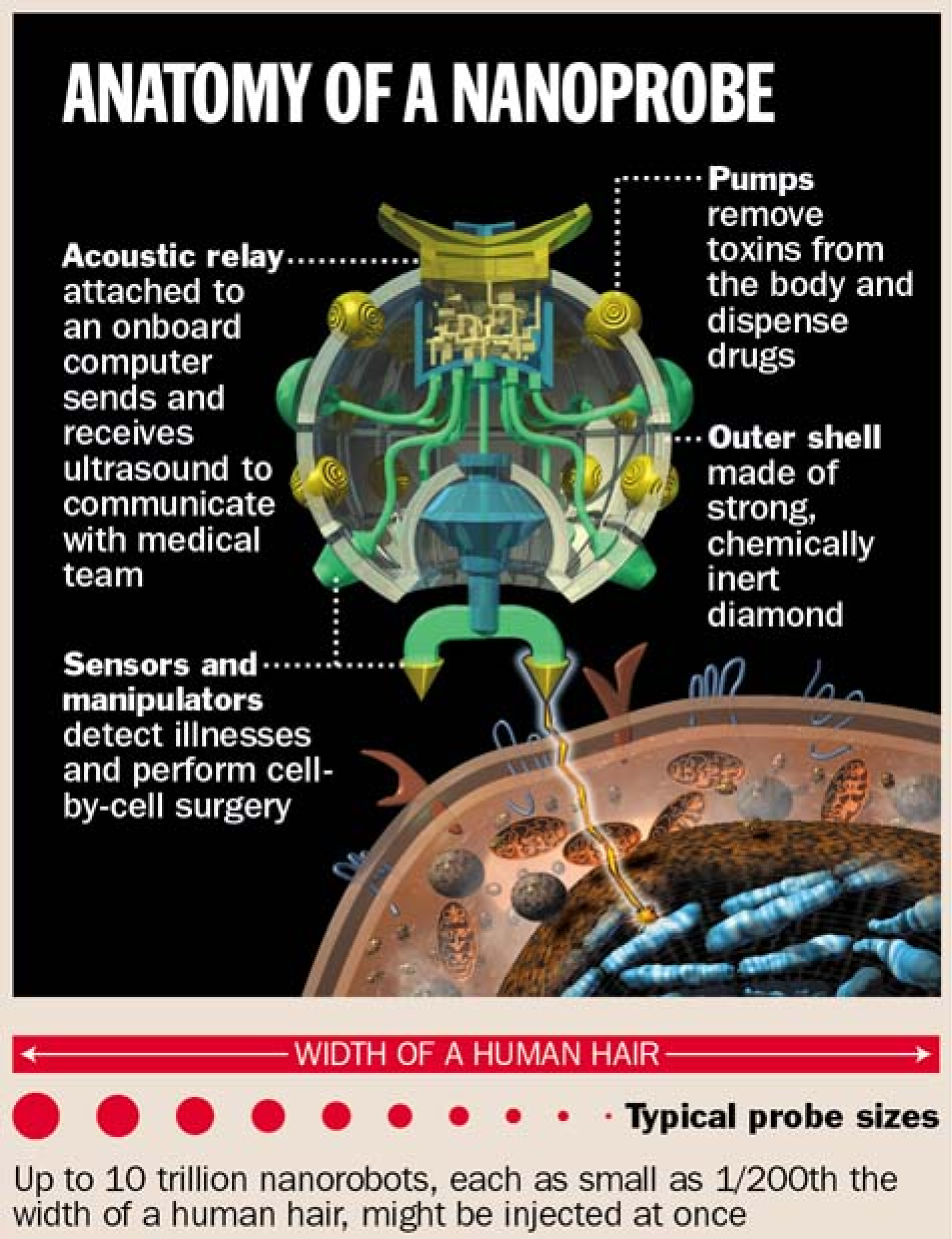
Nanohydraulic piston



Nanorobots for Cell Repair






ANATOMY OF A NANOPROBE
Acoustic relay attached to an onboard computer sends and receives ultrasound to communicate with medical team
Pumps remove toxins from the body and dispense drugs
Outer shell made of strong, chemically inert diamond
Sensors and manipulators detect illnesses and perform cell-by-cell surgery
WIDTH OF A HUMAN HAIR
Typical probe sizes
Up to 10 trillion nanorobots, each as small as 1/200th the width of a human hair, might be injected at once

US National Nanotechnology Intiative: R&D targets by 2015

- Nanoscale visualization and simulation of 3-D domains
- Transistor beyond/integrated CMOS <10nm
- New catalysts for chemical manufacturing
- No suffering and death from Cancer Tx
- Control of nanoparticles in air, soils, and waters
- Advanced materials and manufacturing: ½ from molecular level
- Pharmaceuticals synthesis and delivery: ½ from nanoscale level
- Converging technologies from nanoscale
- Life-cycle biocompatible/sustainable development
- Education: nanoscale vs. microscale based

National Cancer Insitute: Nanotechnology & Nanomedicine

NATIONAL CANCER INSTITUTE

Acknowledgements

- Babak Kateb (COH)
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- Mike Chen (COH)
- Michael J. Bronikowski (NASA-JPL)
- Harish Manohara (NASA-JPL)
- Behnam Badie (COH)

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4*. Winter PM, Cai K, Chen J, Adair CR, Kiefer GE, Athey PS, Gaffney PJ, Buff CE, Robertson JD, Caruthers SD, Wickline SA, Lanza GM. Targeted PARACEST nanoparticle contrast agent for the detection of fibrin. *Magn Reson Med.* 2006 Dec;56(6):1384-8.

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7. Kateb B, Van Handel M, Zhang L, Bronikowski MJ, Manohara H, Badie B. Internalization of MWCNTs by microglia: Possible application in immunotherapy of brain tumors. Neuroimage. 2007 May 13.

- Mulder WJ, Douma K, Koning GA, van Zandvoort MA, Lutgens E, Daemen MJ, Nicolay K, Strijkers GJ. Liposome-enhanced MRI of neointimal lesions in the ApoE-KO mouse. *Magn Reson Med.* 2006 May;55(5):1170-4.
- Mulder WJ, Strijkers GJ, van Tilborg GA, Griffioen AW, Nicolay K. Lipid-based nanoparticles for contrast-enhanced MRI and molecular imaging. *NMR Biomed.* 2006 Feb;19(1):142-64.

Liu Y, Miyoshi H, Nakamura M. Nanomedicine for drug delivery and imaging: a promising avenue for cancer therapy and diagnosis using targeted functional nanoparticles. Int J Cancer. 2007 Jun 15;120(12):2527-37.

Hughes GA. Nanostructure-mediated drug delivery. Nanomedicine. 2005 Mar;1(1):22-30.

Questions?

biophysics

- Uiuc nanotube
- http://www.ks.uiuc.edu/Highlights/?section=2005&highlight=2005-01a
- Thinkquest.org: nanomed picture

Swiss nano insitute

- http://www.nccr-nano.org/nccr/media/gallery/gallery_01/gallery_01_06
- Inorganic nanowires
- http://www.nccr-nano.org/nccr/media/contacts
- http://www.nccr-nano.org/nccr/media/gallery/gallery_01/gallery_01_03#pics_07

nanoglossary

- http://www.nanotech-now.com/nanotechnology-glossary-M-O.htm

NIBIB/NIH Programs for Image-Guided Surgery

John Haller, Ph.D.
National Institute of Biomedical Imaging and Bioengineering
National Institutes of Health

Mission of NIH

Its mission is….to extend healthy life and reduce the burdens of illness and disability.

NIH is the steward of medical and behavioral research for the Nation.

Mission of the NIBIB

To improve health by leading the development and accelerating the application of biomedical technologies.

The Institute is committed to integrating the physical and engineering sciences with the life sciences to advance basic research and medical care.

NIBIB Scientific Research Program Areas

http://www.nibib.nih.gov/Research/ProgramAreas

NIBIB Programs for Image-Guided Interventions

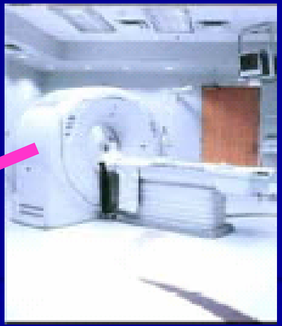
Objectives

- Foster the invention and development of innovative, minimally invasive image-guided procedures to replace traditional surgery and invasive techniques.
- Enable new, faster and more precise treatment and biopsy procedures that minimize unintended damage to healthy tissue.
- Integrate multi-dimensional data from complimentary sources including MR, CT, nuclear, optical or ultrasound for real-time guidance

National Institute of Biomedical Imaging and Bioengineering

National Institute of Biomedical Imaging and Bioengineering

Image-Guided Surgery



- Image-guided surgery requires:
  - a source of images
  - linked to the patient
  - target definition in the real 3D patient
  - related to the virtual image.

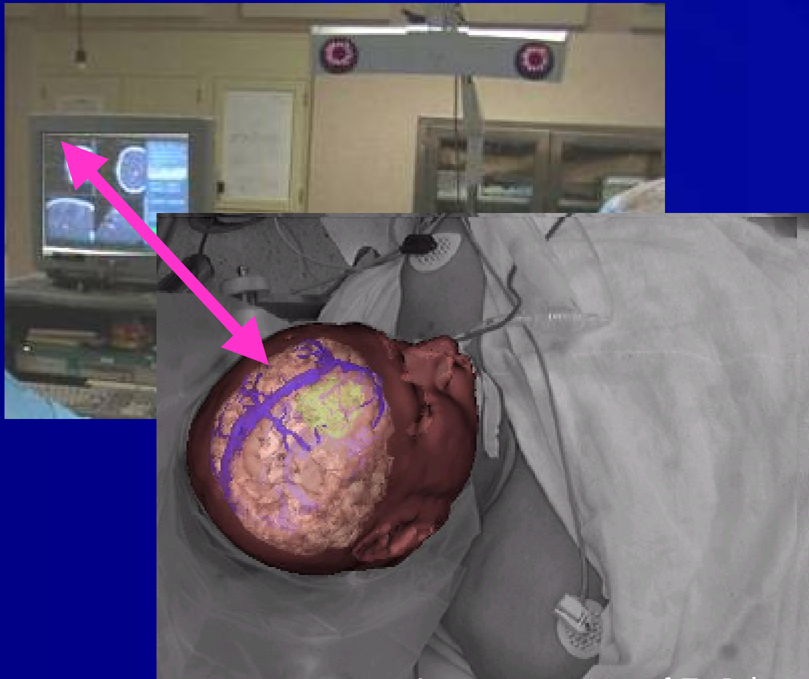


Image courtesy of F. Jolesz

NIBIB Past Requests for Applications (RFAs) for Image-Guided Interventions

2003 RFA

Image-Guided Interventions

- $5M/yr set aside
- R21s and R01s awarded

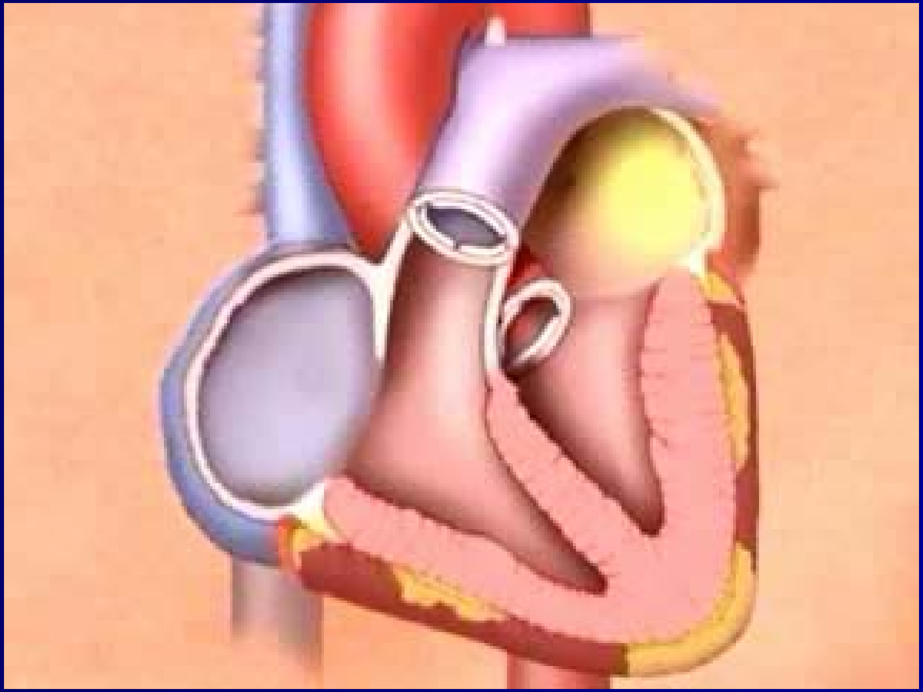
2007 RFA

Technology Development of Image-Guided Interventions: Phase I (R21)

- $5M/yr set aside
- 11 R21s, $300K per year direct costs
- First phase of a two-phase project to deliver high clinical impact, disruptive technologies for image-guided interventions

RF Ablation to correct abnormal heart rhythm

Richard Robb, Mayo Clinic

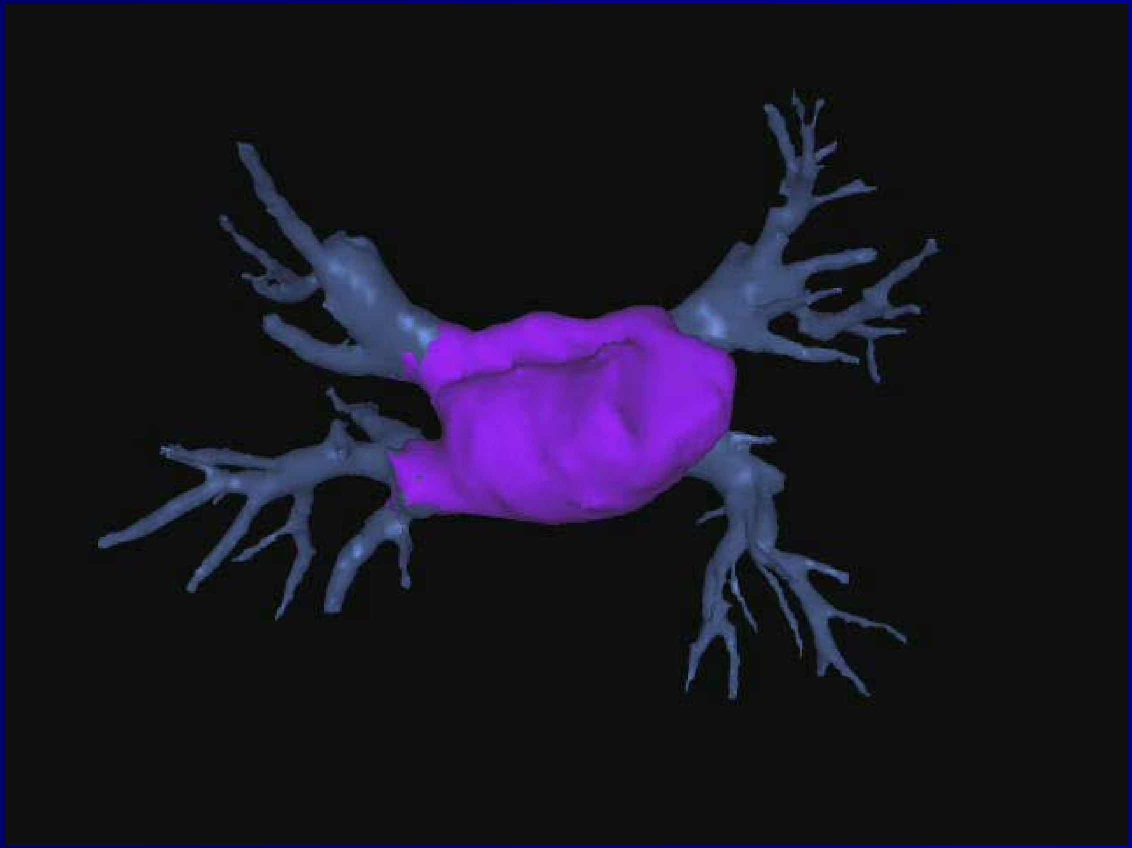


Potentially life-threatening cardiac arrhythmias can be corrected by minimally invasive procedures whereby an ablation electrode is introduced into the heart through a catheter and used to destroy anomalies in the heart’s 'wiring'.

5-D Image-Guided Cardiac Ablation:

Improved visualization can significantly reduce treatment time

Richard Robb, Mayo Clinic

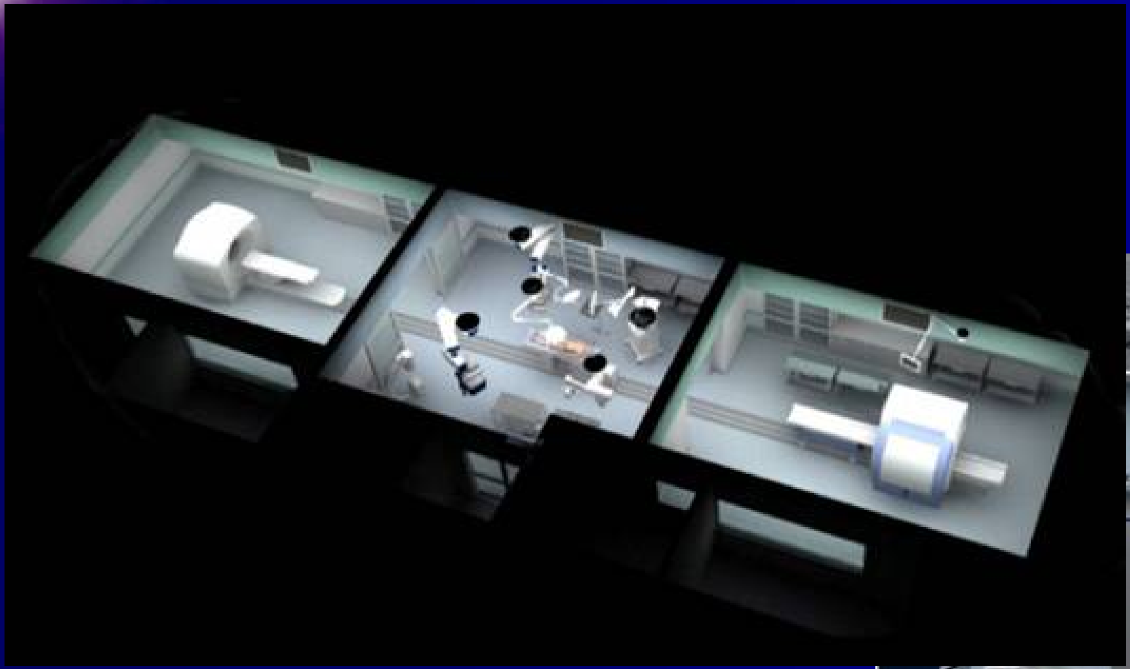


Electrophysiology is used to locate areas of heart's atrium that give rise to the abnormal electrical impulses that cause arrhythmias. Electrical flow information is then used to guided treatment (RF ablation) of the abnormal tissue.

2007 RFA
Technology Development of Image-Guided Interventions: Phase I (R21)

ARMAND, MEHRAN	JOHNS HOPKINS UNIVERSITY	Image-Guided Osteoporotic Bone Augmentation with Intraoperative Biomechanical Guidance
TEARNEY, GUILLERMO	MASSACHUSETTS GENERAL HOSPITAL	Miniature Laser Therapy Endoscope
NEVO, EREZ	ROBIN MEDICAL, INC.	MRI-mediated radiofrequency ablation
PAULY, JOHN M.	STANFORD UNIVERSITY	MRI-Guided, Robotically Controlled Cardiac Ablation
GOUNIS, MATTHEW	UNIV OF MASSACHUSETTS MED SCH WORCESTER	Mechanical Clot Obliteration for the Treatment of Stroke
FRANGIONI, JOHN	BETH ISRAEL DEACONESS MEDICAL CENTER	Spatially Modulated Near-Infrared Light for Image-Guided Cancer Surgery
WOLF, PATRICK D	DUKE UNIVERSITY	Ultrasound Based Multimodal Imaging System for Guiding Cardiac Ablation Therapy
STETTEN, GEORGE	UNIVERSITY OF PITTSBURGH AT PITTSBURGH	Holographic Sonic Flashlight for Guiding Interventional Procedures
PAPADEMETRIS, XENOPHON	YALE UNIVERSITY	Image-Guided Deep Brain Microscopy for Neurosurgical Intervention
MIGA, MICHAEL	VANDERBILT UNIVERSITY	Correcting for Soft Tissue Deformation in Image-Guided Liver Surgery
FOWLER, DENNIS	COLUMBIA UNIVERSITY HEALTH SCIENCES	Image Guided In Vivo Tooling Platform for Minimal Access Surgery

National Center for Image-Guided Therapy
Ferenc Jolesz, Brigham and Women's Hospital

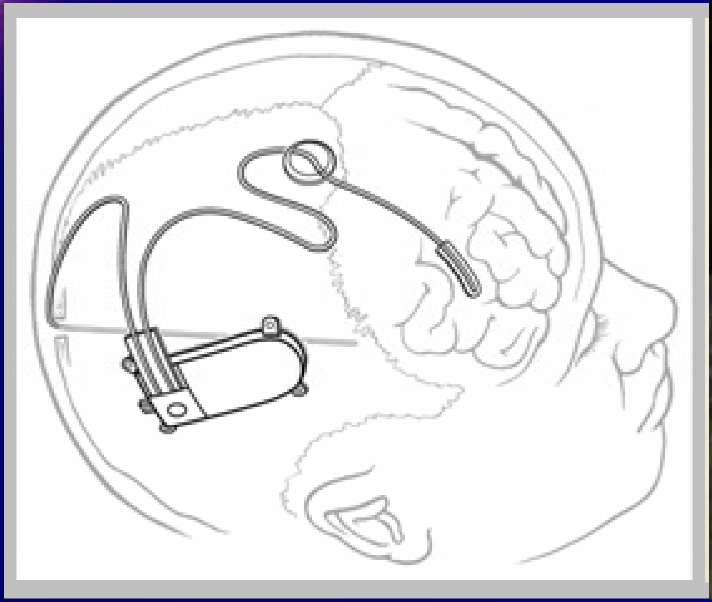


National Institute of Biomedical Imaging and Bioengineering

Bioimaging and Intervention in Localization-Related Epilepsy

James Duncan, Yale University

2-R01-EB000473-06



Responsive Neurostimulator (RNS)

Continuously monitor electrical activity

Detect suspected seizure onset: deliver brief and mild electrical stimulation to suppress the seizure.

National Institute of Biomedical Imaging and Bioengineering

BECON Biomedical Engineering Research Funding Opportunities

- Exploratory/Developmental (R21) Bioengineering Research Grants - PA-06-058 - Released May 24, 2006 Receipt Dates: Standard R21 Receipt Dates
- Bioengineering Research Grants (BRG) - PA-06-419 - Released May 17, 2006 - Receipt Dates: February 1, June 1 and October 1
- Bioengineering Research Partnerships - PAR-06-459 – Released June 12, 2006 – Replaces PAR-04-023 - Receipt dates: September 20, 2006 and January 22, 2007. Letter of Intent Receipt dates: August 20, 2006 and December 20, 2006

NIH Grant Applications

Most important are….
investigator-initiated (unsolicited) grants

You don’t have to fit into an initiative
….we want to help you get YOUR best ideas funded

Life Cycle of a Grant Application

(Investigator-initiated or responding to announcements)

PI

Receipt and Referral

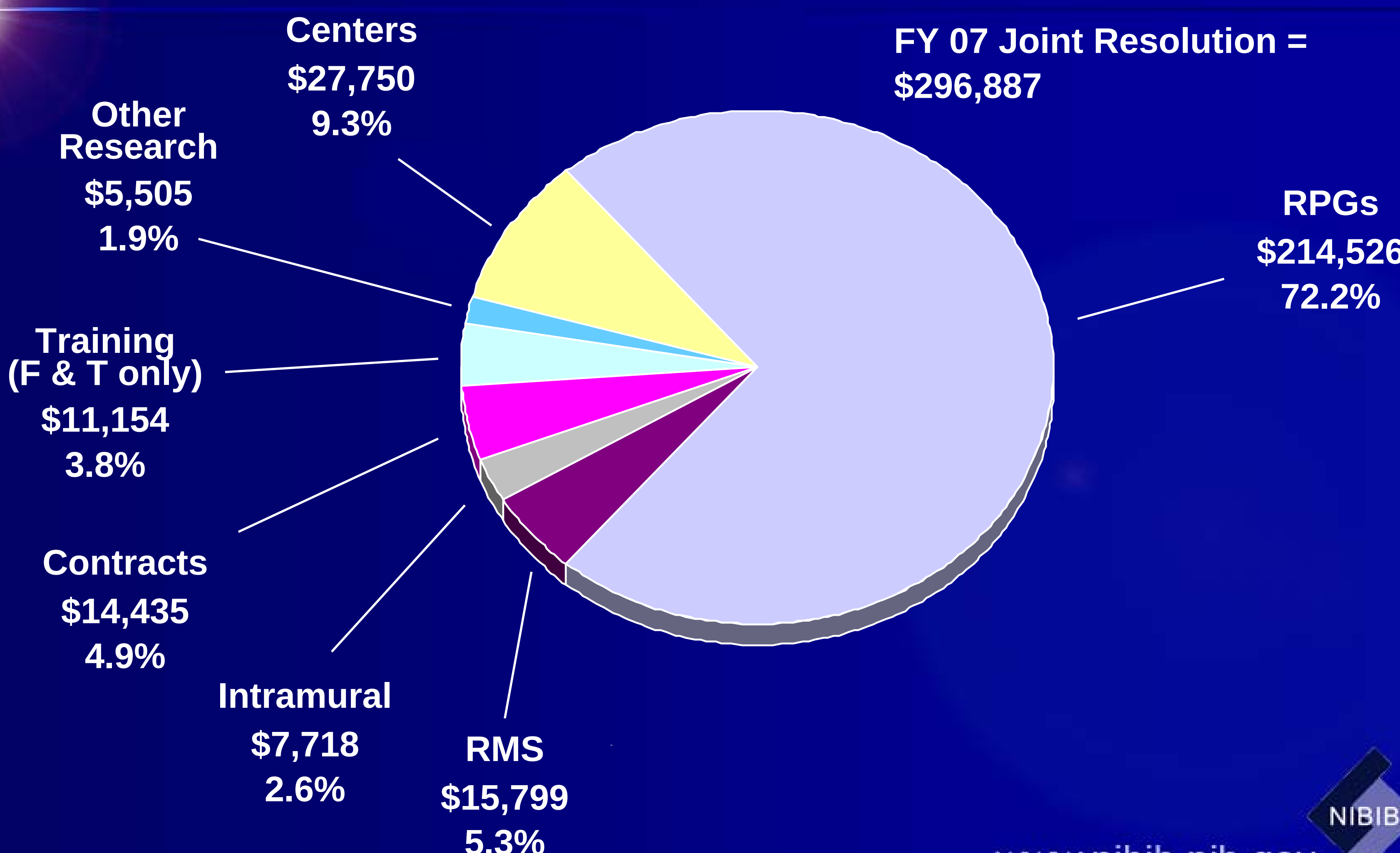
Scientific Review Groups

Three overlapping receipt cycles per year

Funding Decision by IC's National Advisory Council, based on Priority Score and Program Priorities

FY 2007 NIBIB Budget

(Dollars in Thousands)



National Institute of Biomedical Imaging and Bioengineering

NIBIB FY07 Pay Plan

19th Percentile for R01s, R21s

New Investigator Policy

Additional 5% for new investigator R01

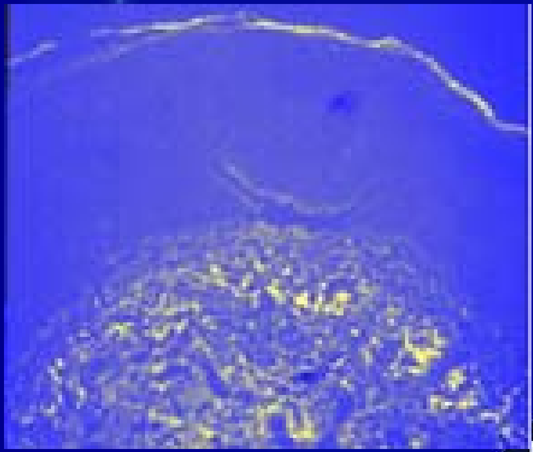
Scientific Goals
NIBIB Strategic Plan, 2005-2010

- A strong extramural research community focused on … science and technology to improve health.
  - Support investigator-initiated projects
- Targeted research programs
- Accelerate translation of promising technologies
- Reduce health disparities through new and affordable medical technologies

Appropriate technology for cervical cancer detection

- A new cervical cancer detection method uses a small fiber optic probe

- Developed by Rebecca Richards-Kortum, Rice Univ., Chair of Biomedical Engineering



National Institute of Biomedical Imaging and Bioengineering

John Haller hallerj@mail.nih.gov

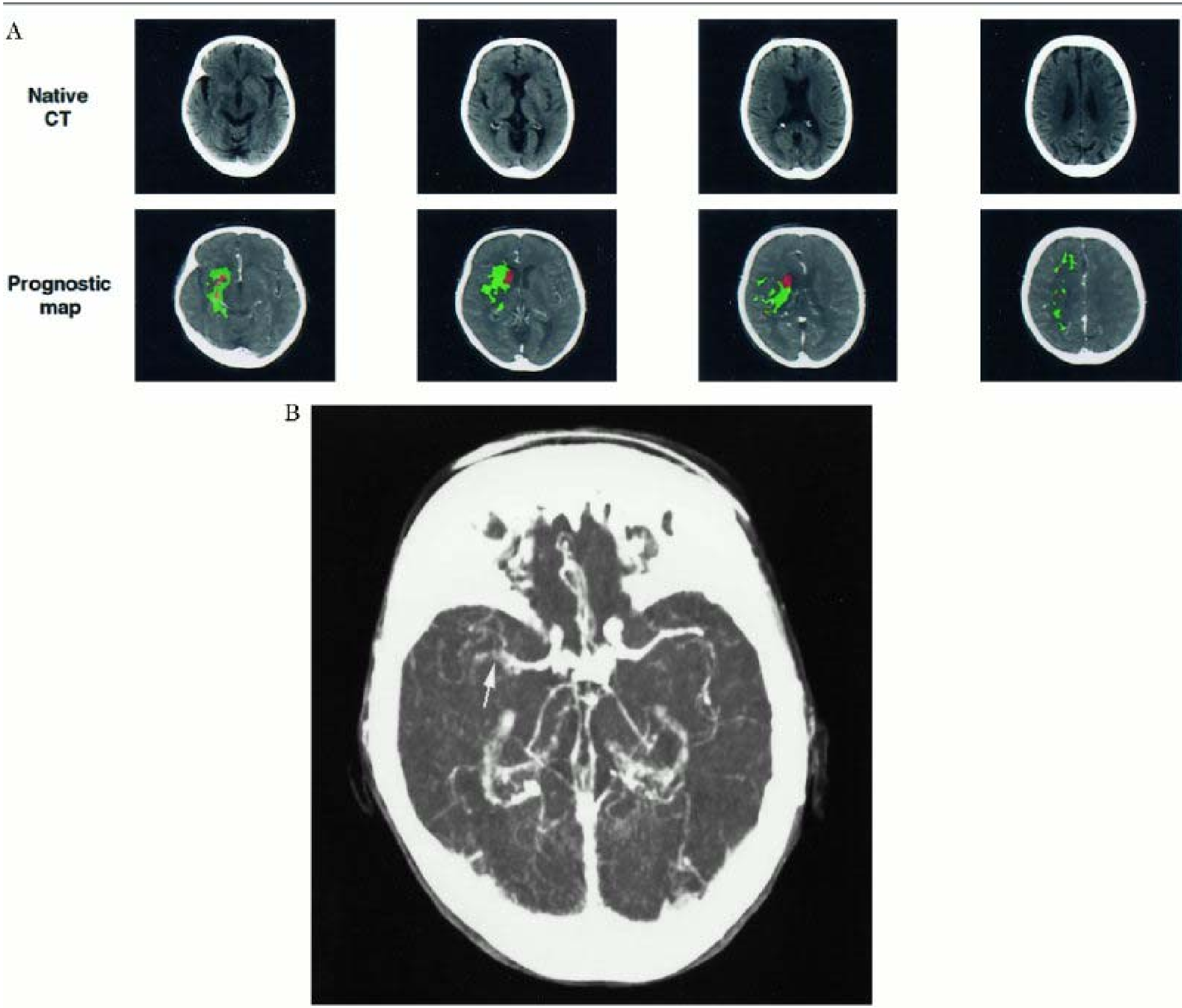
NIBIB

www.nibib.nih.gov

Progress and hurdles in mapping stroke.

Walter J. Koroshetz, M.D.
National Institute of Neurologic Diseases and Stroke
Work of the MGH stroke and neuroradiology services
Martinos MRI Center

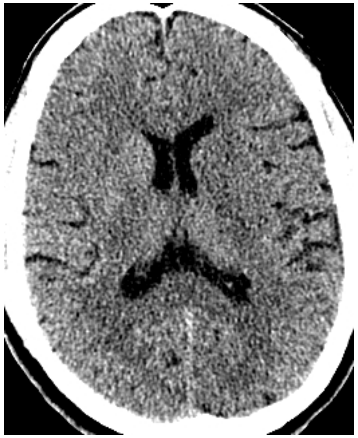
Acute pre lysis scan: 5 hrs of onset



Acute Stroke Imaging in the Best of All Possible Worlds: The Questions.

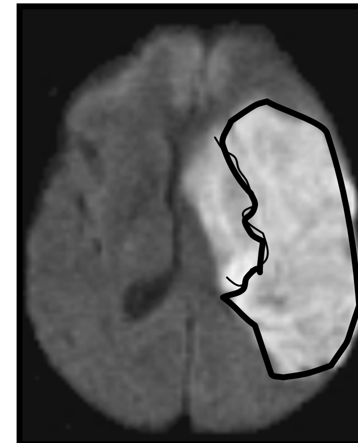
- **Blood or no blood** 
- **Vascular Lesion** 
- **Risk of hemorrhage** with reperfusion ± ☑
- **Ischemia?** Mapping regions are at risk of infarction. ±
- **Infarction?** Mapping already infarcted regions (not salvageable by reperfusion). ±
- **Functional outcome** prediction based on maps of infarct/salvageable tissue -

CT and MR imaging of penumbra?

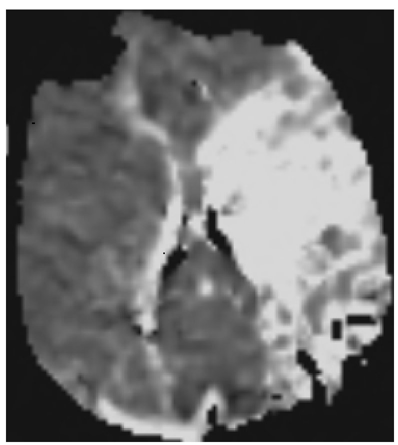

Acute CT

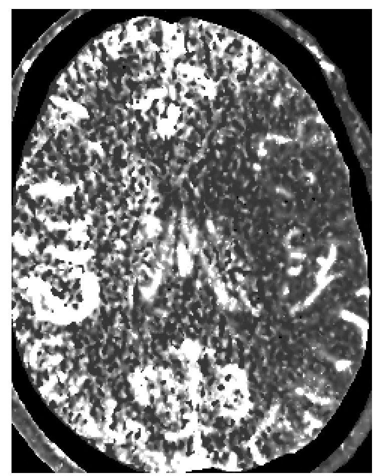

Acute CTA-SI

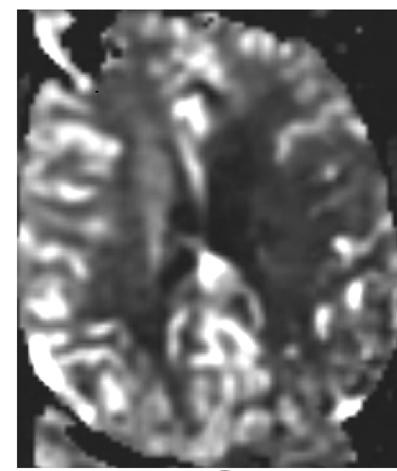

Acute DWI


Final


CT MTT


MR MTT


CT CBF

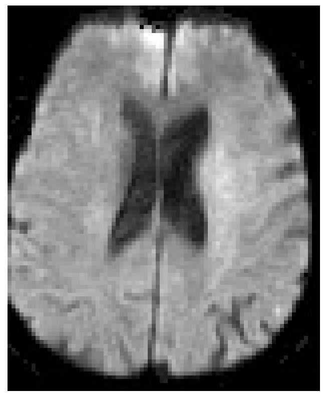

MR CBF

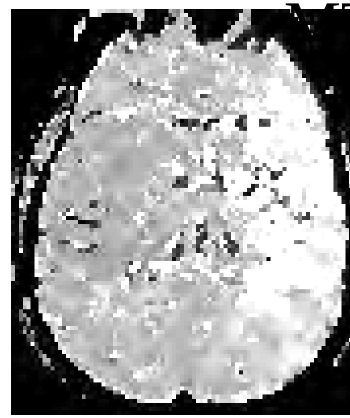
Mismatch and Salvage by IA lysis

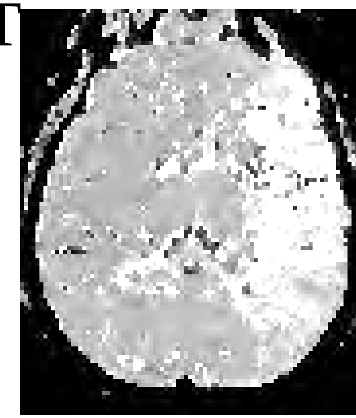
DWI

MTT

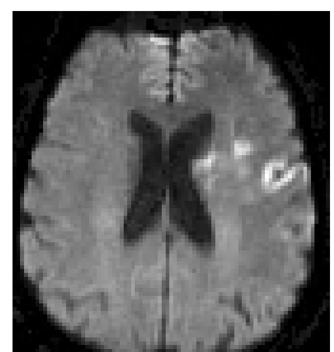
Pre

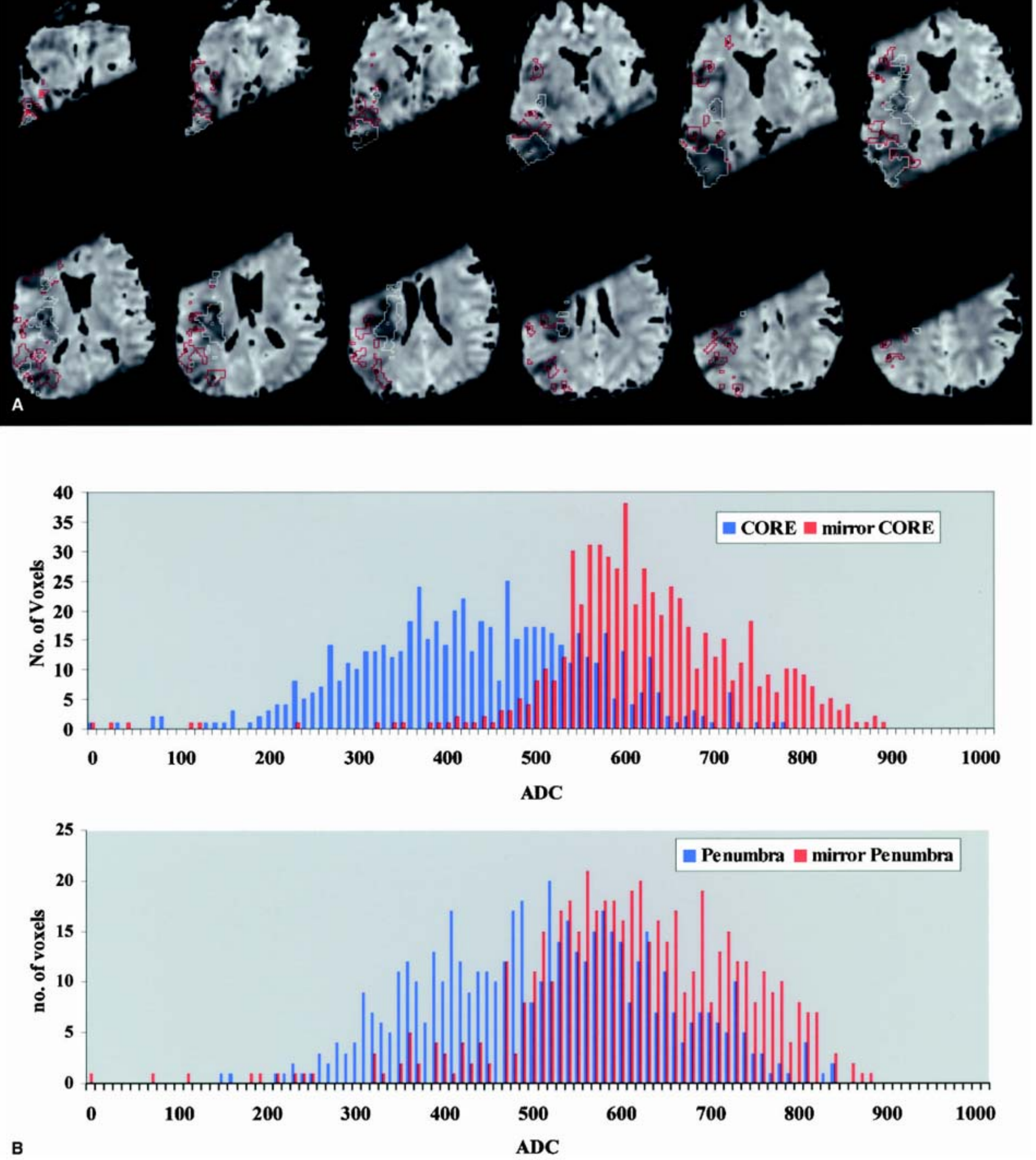






Post IA





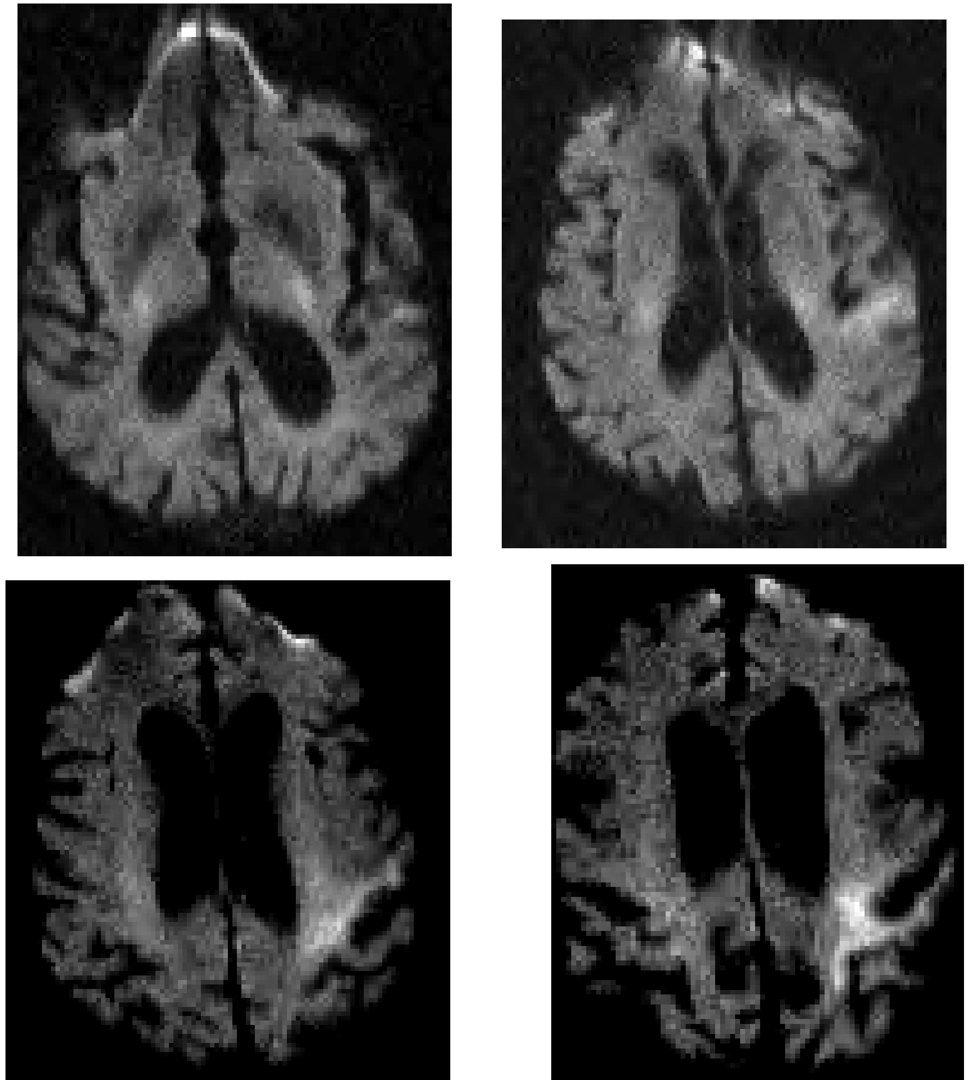
PET vs DWI

- Guadango et. Al. JCBFM 24:1249: 2004

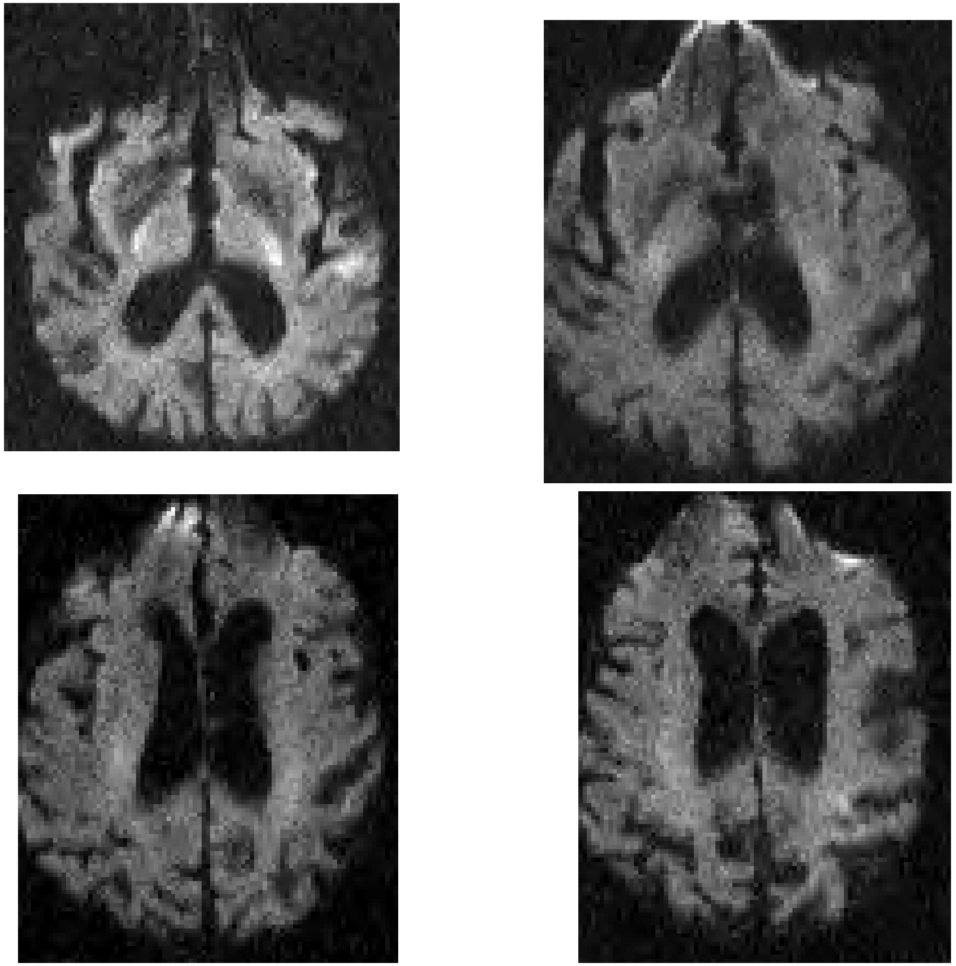
PET defined core with lower average ADC values, but overlap with normal ADC distribution

PET defined penumbra includes some regions with low ADC

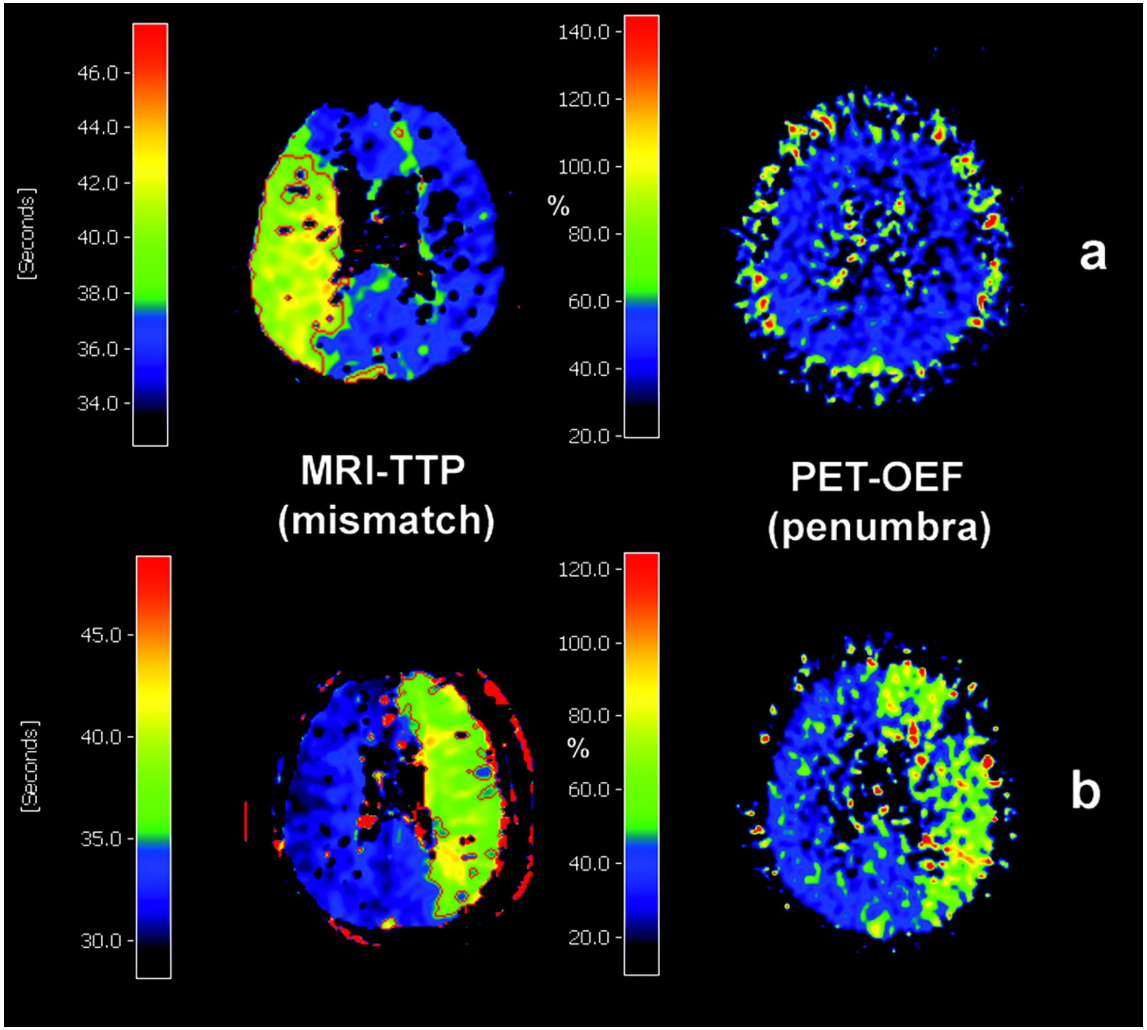
1st DWI Pridg



Repeat DWI after rt-PA Pridg



Volumetric comparison of TTP (MRI) and OEF (PET) images in 2 patients measured in the chronic phase of stroke

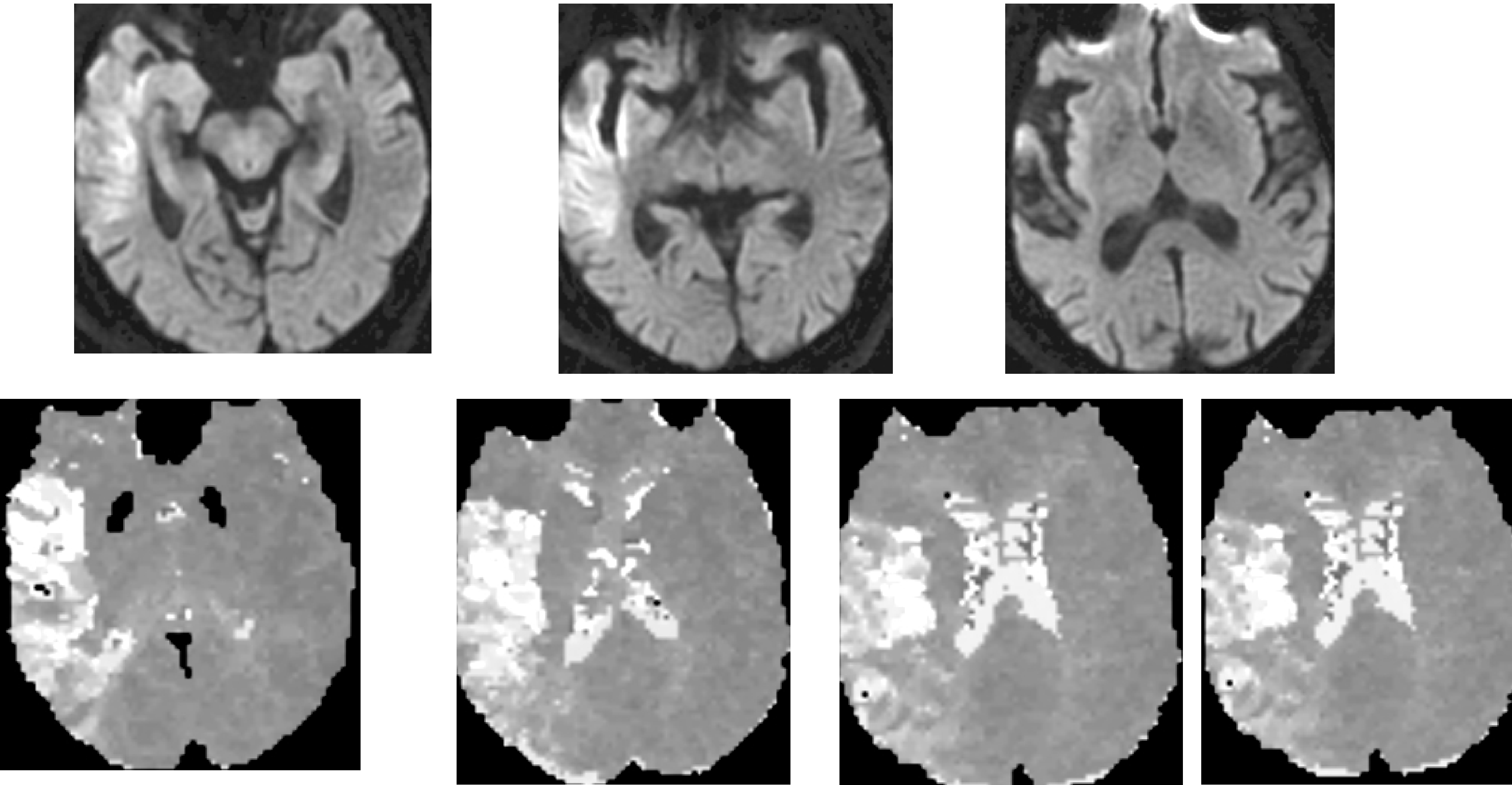


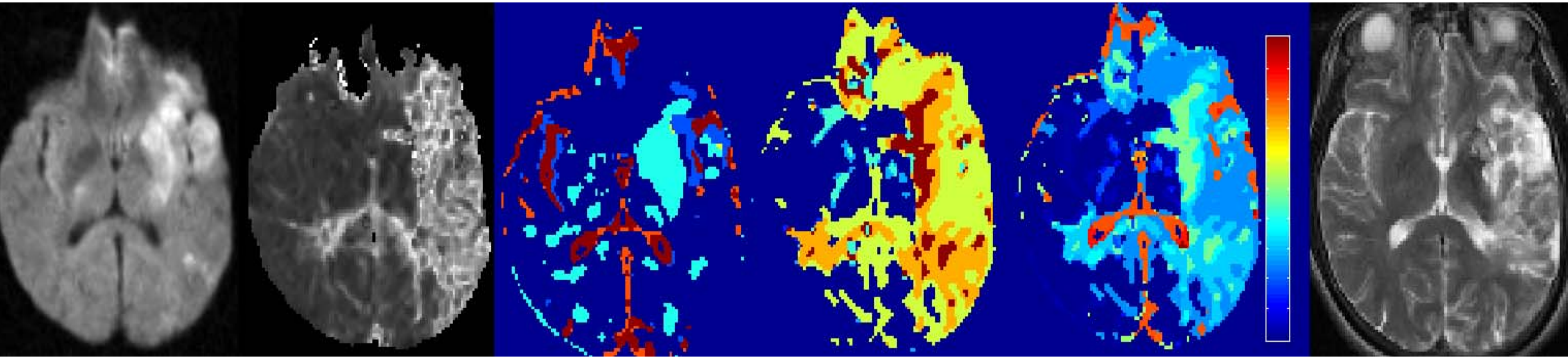
Sobesky, J. et al. Stroke 2005;36:980-985

Stroke

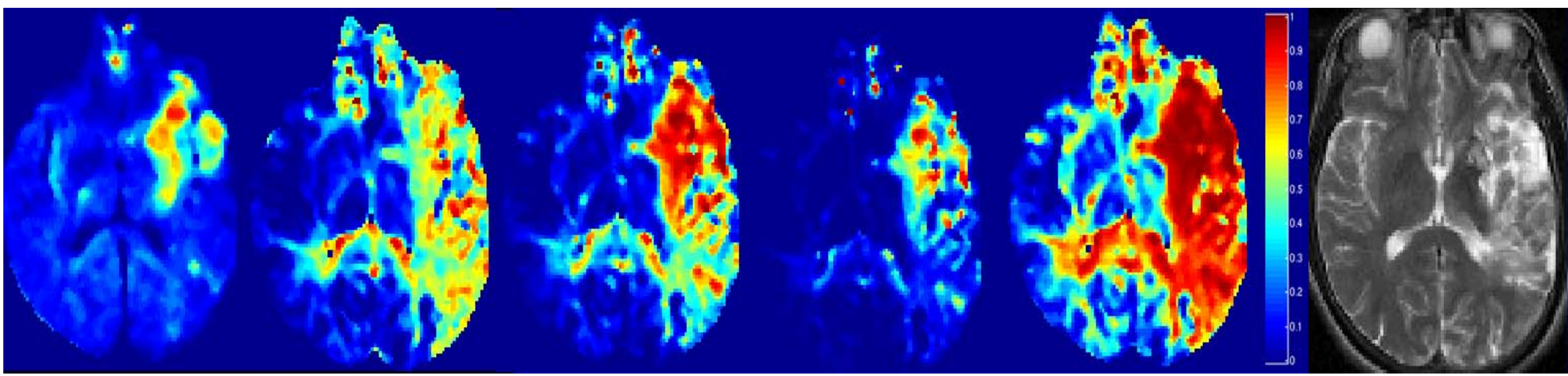
American Stroke Association® A Division of American Heart Association

Large Mismatch but really not tissue “at risk”; NIHSS=4





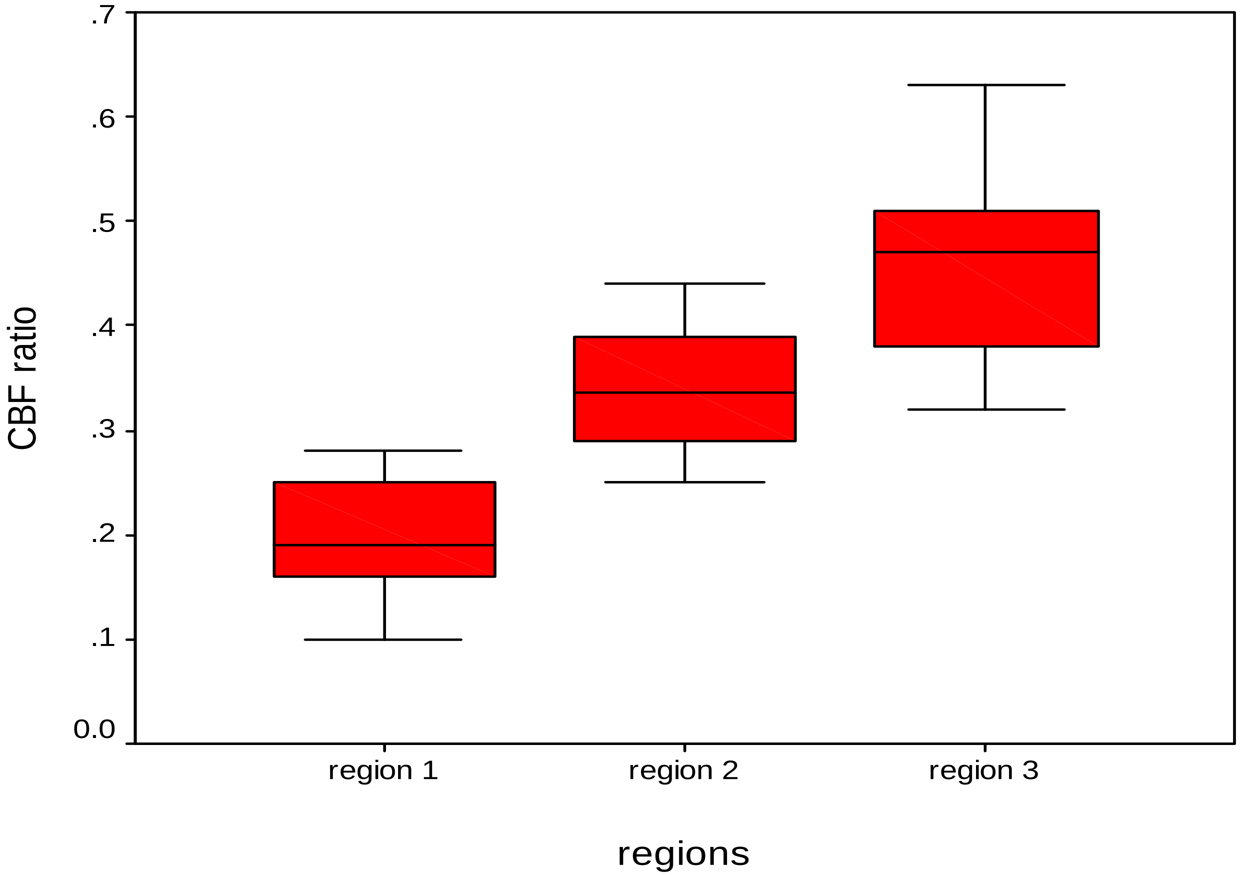
DWI MTT



ADC+T2 rCBV+rCBF All 95% CI: lower 95% CI: upper

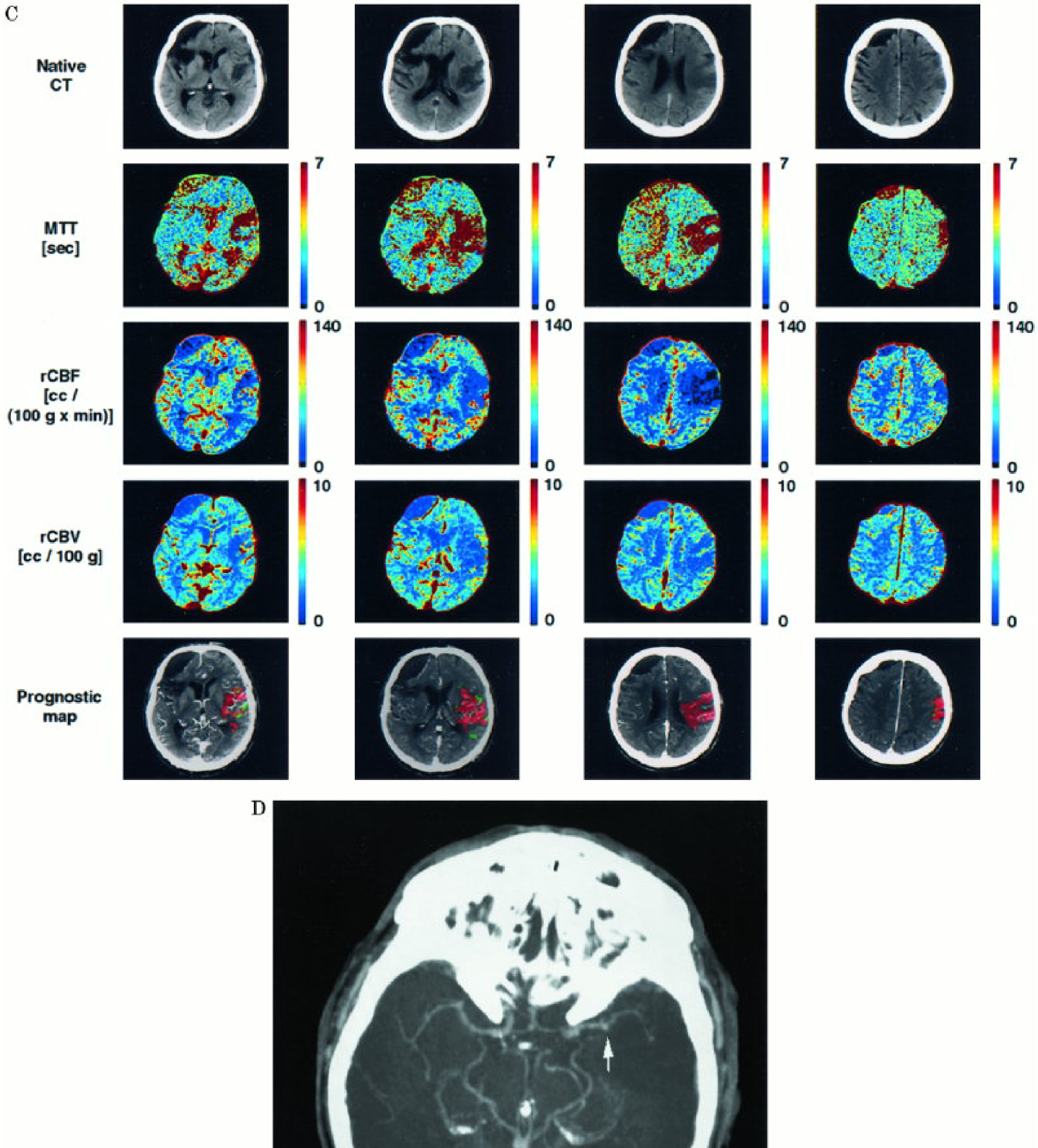
Follow-up

IA lysis cases: CBF in core, lost, and salvaged regions Pamela Schaefer, Luca Roccatagliata



Follow up study:

28 hours



Converting from brain maps to functional outcome

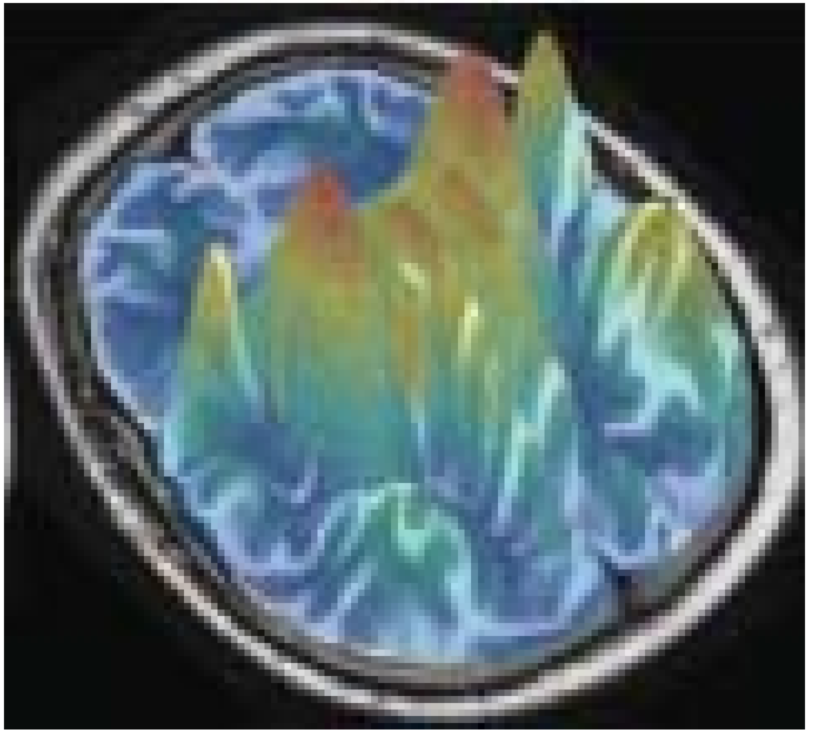
- Clinical question: is it worth the risk to attempt to reperfuse the salvageable tissue.
  - Depends upon:
    - Volume of tissue
    - Location of tissue
    - Recovery process
    - Unknowns?

Functional correlate of salvaging tissue

Risk of reperfusion injury- ie. hemorrhage, brain edema,

NIH scores mapped to brain region affected by infarct.

Menezes et. al. Stroke 2007; 38:197



The vertical dimension is colorized to indicate relative impact in NIHSS units , more red =greater deficits.

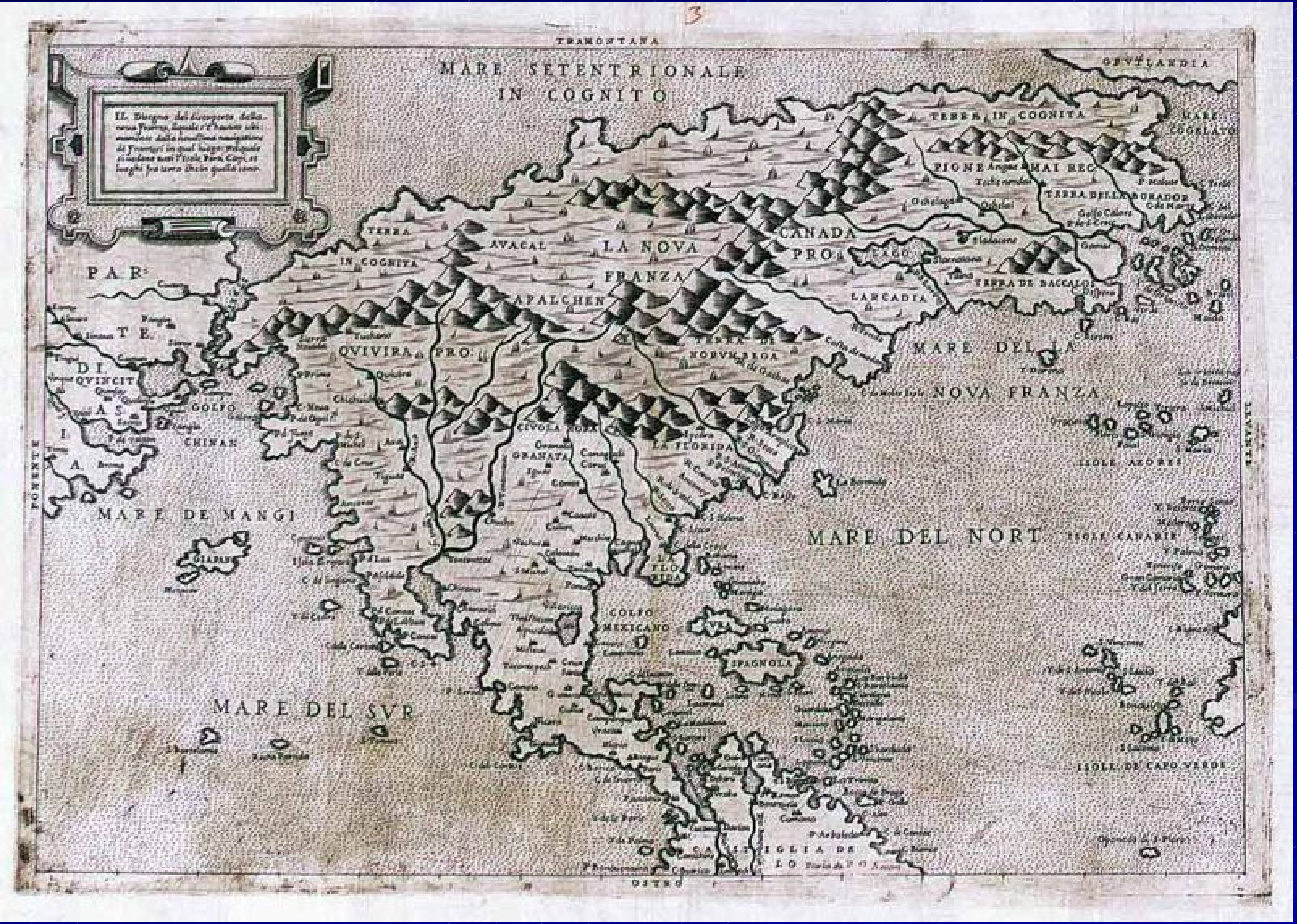
Future

- Prediction of a patient’s functional deficits with and without therapy balanced by assessment of risk of therapy related complication.
- Multifactorial model based on brain maps that predict infarction and functional benefits of reperfusion.

Terra incognita: imaging research opportunities directed toward a better understanding of the *assembly* of the human brain

Authors: Christian Macedonia MD, Jeri Miller PhD, Kenneth Curley MD

Terra incognita



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The TATRC Mission: Re-engineering Medicine

- Proteomics-Genomics
- Advanced Medical Imaging and Image Guided Therapies
- Regenerative Medicine/Bioengineered Tissue Replacements/Cloning
- Medical Robotics and Minimally Invasive Surgery
- Bio-informatics
- Medical Simulation

A METRO Pitch…

Look Familiar?

I 35 Bridge Minneapolis MN

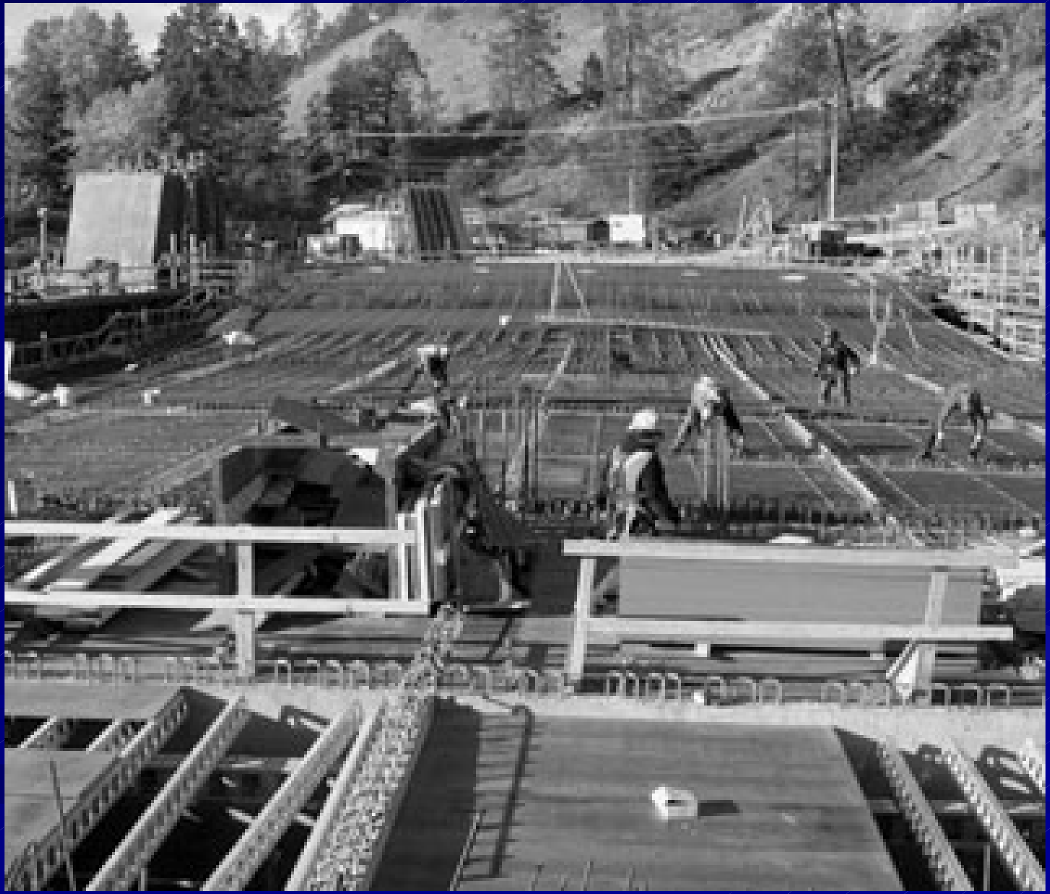
What if…

- A construction worker presents himself to the NTSB investigators and says “I worked on the I-35 bridge construction in the 1960s and I took to work every day one of these….”

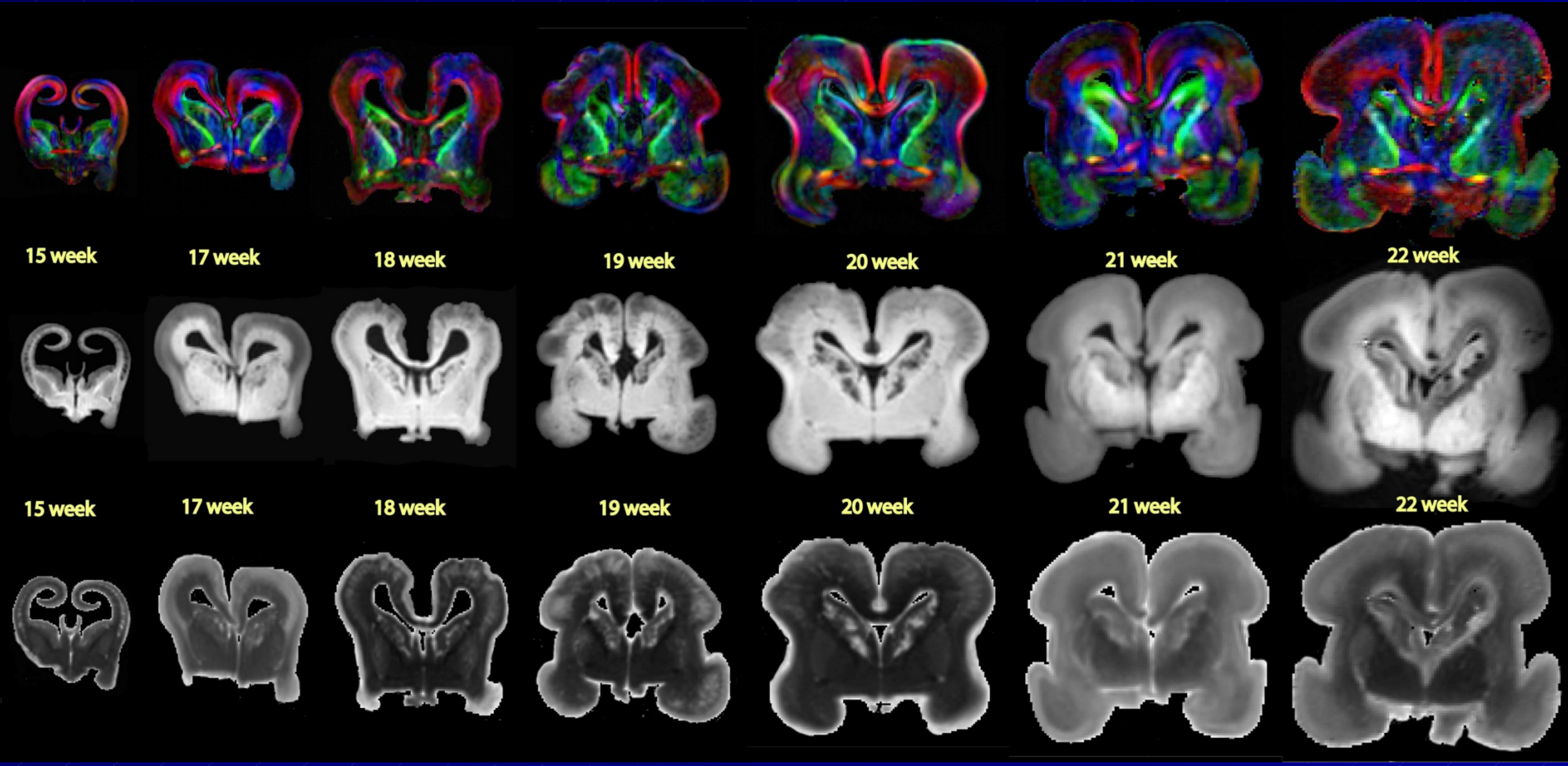
“…and filmed all my friends while they worked on the construction at the site.”

How valuable would those films be now?

How important is knowing the construction methods in understanding prevention of disasters and in optimizing repair?



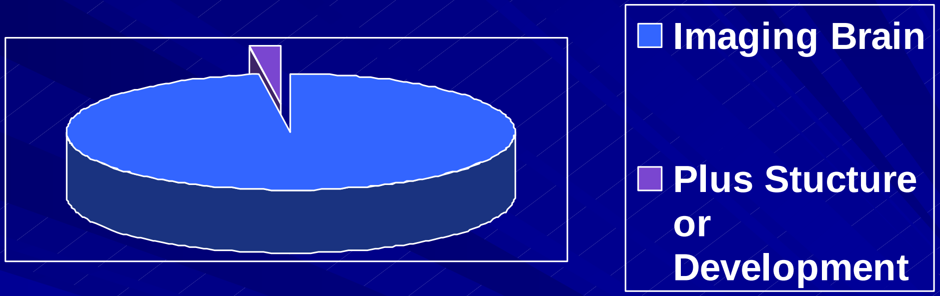
Human brain under construction



http://lbam.med.jhmi.edu/defaultImages/fig1a%20copy.jpg

Perspective

- A calendar year 2007 records search of the MEDLINE PubMed database showed the there are 24 peer reviewed manuscripts indexed for title words “imaging,” “brain,” and “structure,”
- 80 manuscripts indexed for “imaging,” “brain,” and “development.” The majority of these papers have been published only within the past five years.
- 4533 indexed for brain imaging



- There is scant research into the structural development of the human brain correlated to genomic data.
- Most papers detailing genotype-phenotype correlations explore known severe single gene disorders in small case series.

“The Child is the father of the Man.”
William Wordsworth

David Barker CBE

http://www.oundlechronicle.com/articles/newsandsport/330/

http://cuip.uchicago.edu/advwww/98/epullman/premie.jpg

http://www.ast-services.co.uk/casualty-care_clip_image004.jpg

- David Barker and the <u>fetal origins of adult diseases hypothesis</u>. (Barker DJP, ed. Fetal and infant origins of adult disease. London: BMJ Books, 1992)
- Epidemiologist
- Studied the correlation between fetal complications and adult coronary artery disease, impaired glucose tolerance, and hypertension

- Beyond the hypothesis of David Barker that there are many adult diseases with fetal origins, there is an intuitively obvious <u>first principle</u> that if modern medicine hopes to repair adult brains (damaged by war injuries, automobile accidents, stroke, or neurodegenerative disorders) there needs to be a better understanding of how human brains are *assembled*.

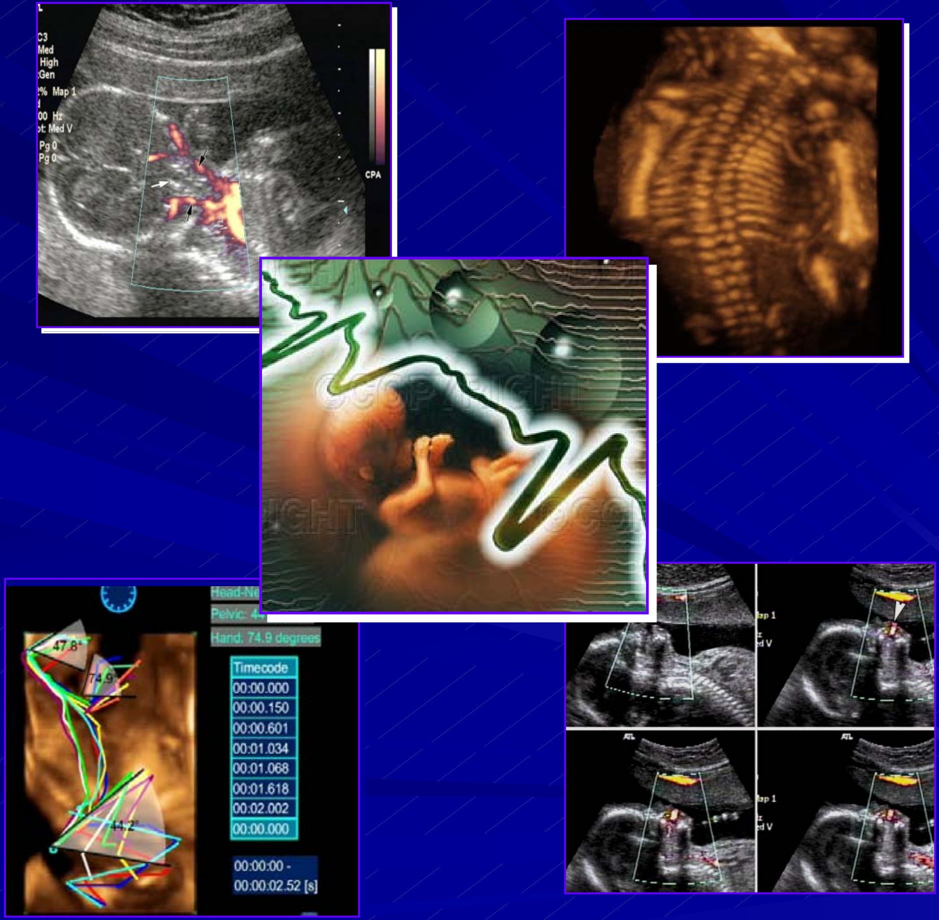
- Opportunities to expand our knowledge on human brain construction exist in the areas of observational imaging research including functional imaging
- Non-invasive perinatal imaging with
  - MRI
  - MRSpectroscopy
  - SQUID
  - 4DUS
- The “omics”; particularly genomics-proteomics, and correlative computer modeling.

If it were easy, it may already have been done…

- Anything involving fetal research is not considered “minimal risk”
- Fetuses develop in their own sequestered compartment surrounded by another person’s tissue
- Functional imaging of a fetus requires a much more interdisciplinary research plan in order to protect the safety of both mother and her developing child..
- Avoidance of ligands, ionizing radiation or high SAR

Sonography

- Identify Interplay of Factors That Drive Development Across Integrated Aerodigestive and Motor Systems Within the Fetal Environment
- Enhance Identification and Quantification of Morphology and Emerging Behavioral Organization

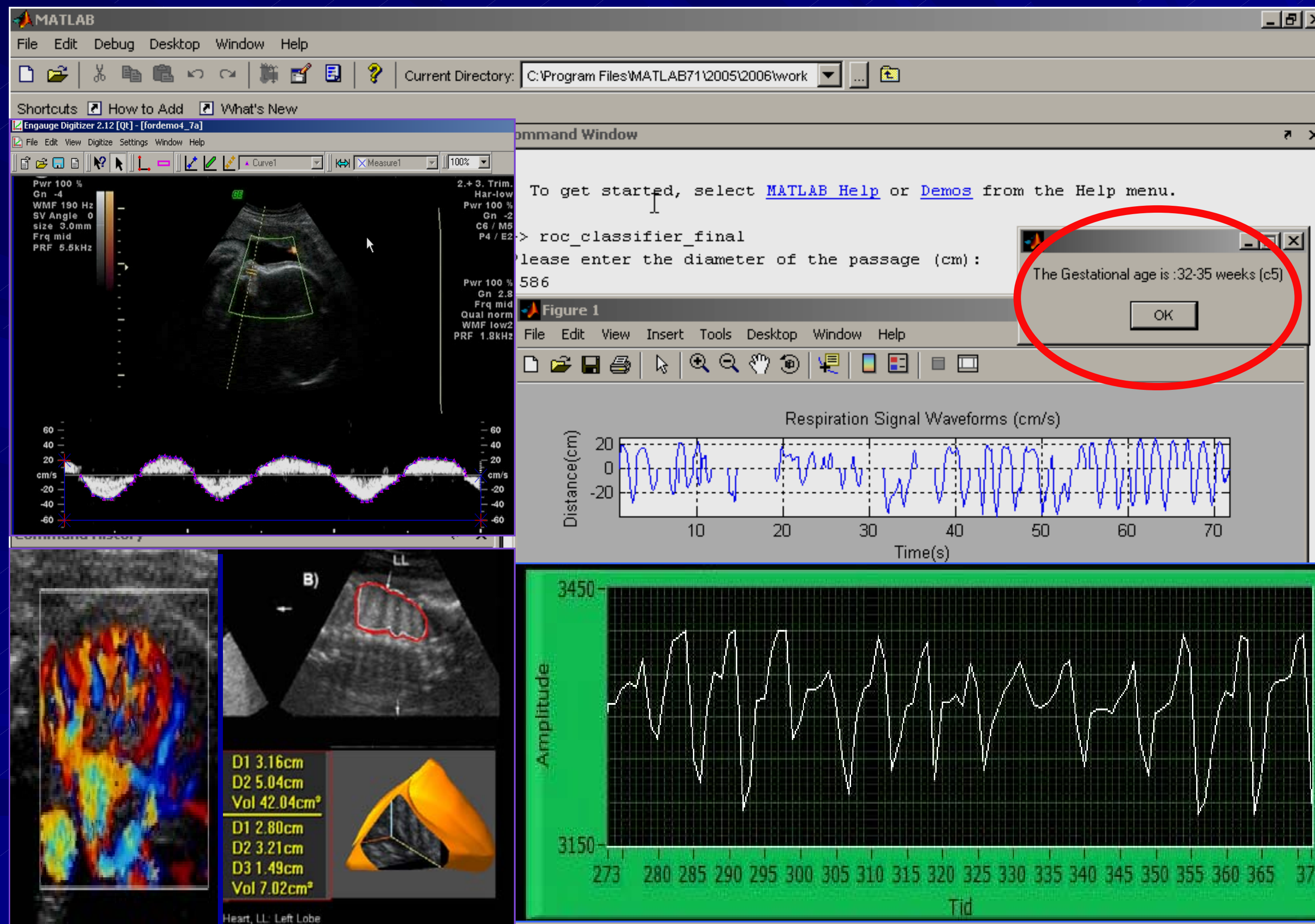


Computer - Aided Diagnosis

- K-Classifiers
- Bayesian Classifiers
- Fuzzy Logic

- Comparison to FLM, L/S Ratios

- 3D Volumes
- Fluid Dynamic Models



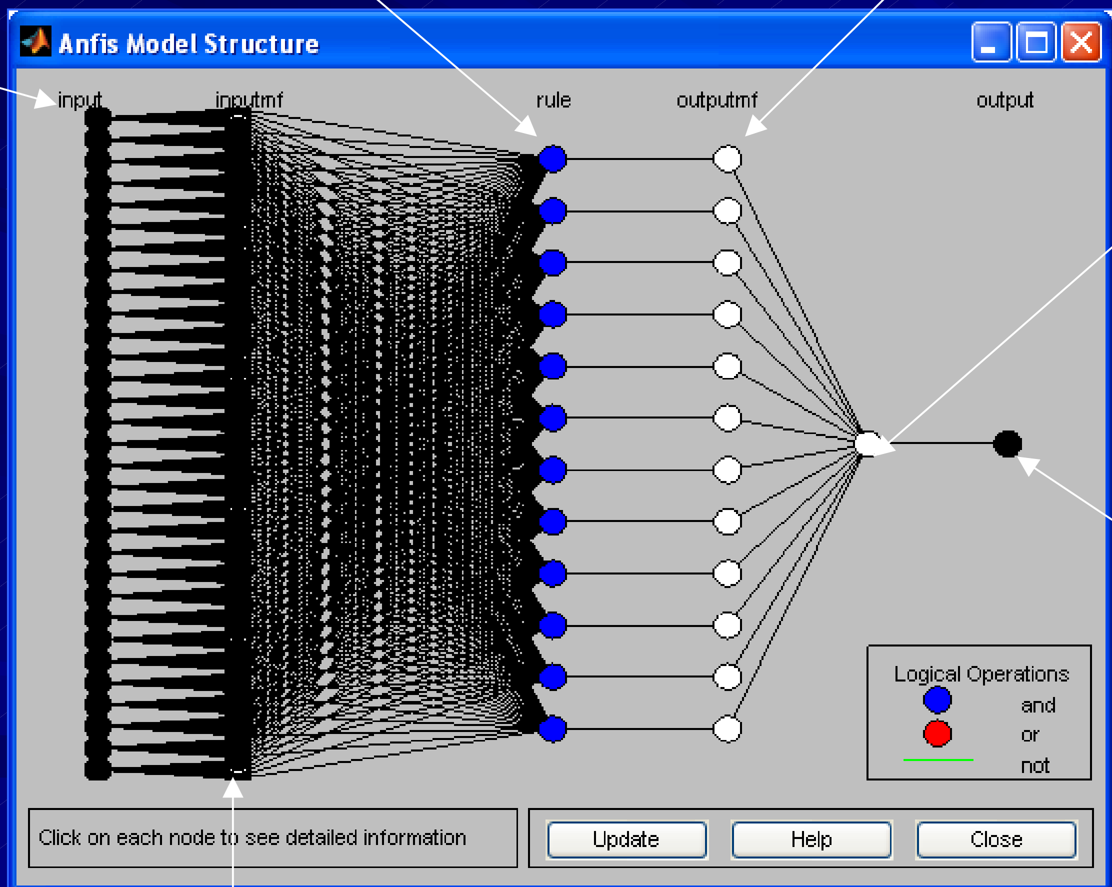
ISBI (2006).

ANFIS: Adaptive Neuro-Fuzzy Inference System *Membership Function for Pathology Classification*

Apply Fuzzy Operator: AND

Obtain One Number That Represents The Result Of The Antecedent For The Rule

Inputs(31 Features)



Aggregation: The Fuzzy Sets That Represent The Outputs Of Each Rule Are Combined Into A Single Fuzzy Set

Defuzzification: Defuzzify The Aggregate Output Fuzzy Set To A Single Number

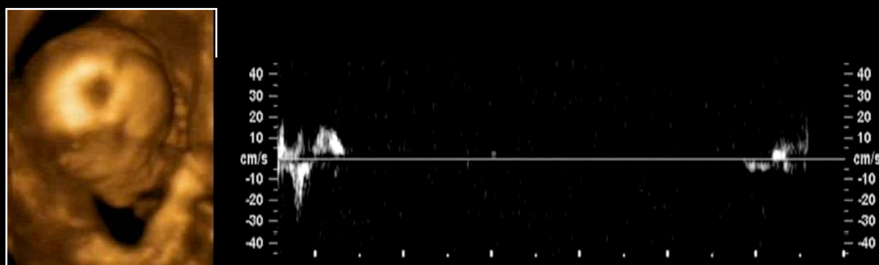
Fuzzify Inputs: Each Input Associated With 3 Membership Functions

(MathWorks, Inc.)

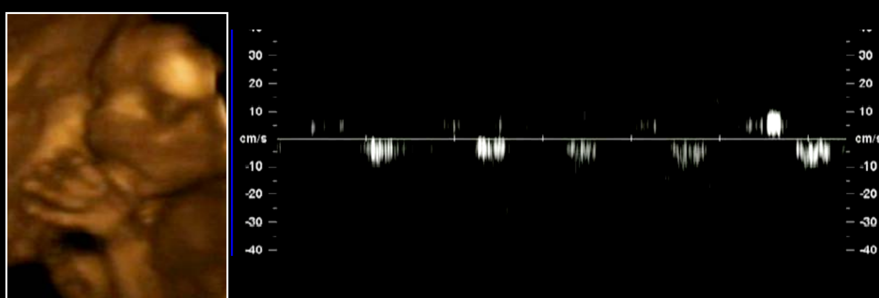
Canalicular (16-26 w):

Airways widen-lengthen leading to potential air space for lungs. Terminal and respiratory bronchioles.

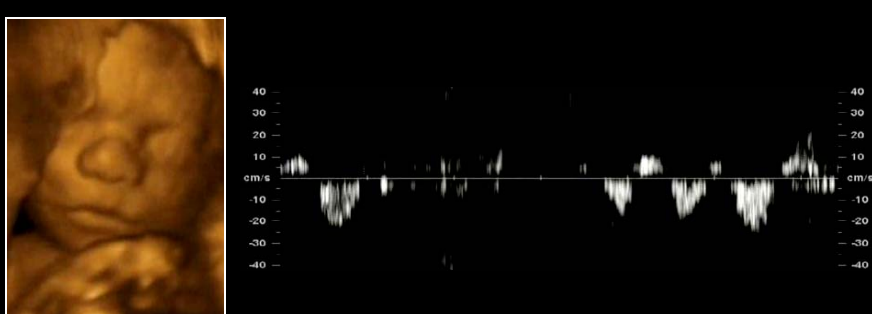
C1: 16.0 - 19.6 w GA



C2 : 20.0 - 23.6 w GA



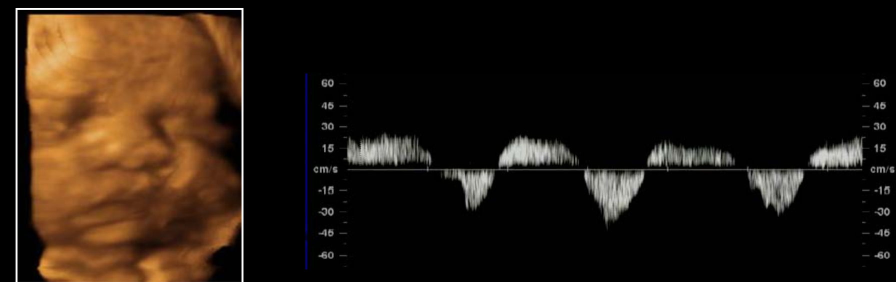
C3 : 24.0 - 27.6 w GA



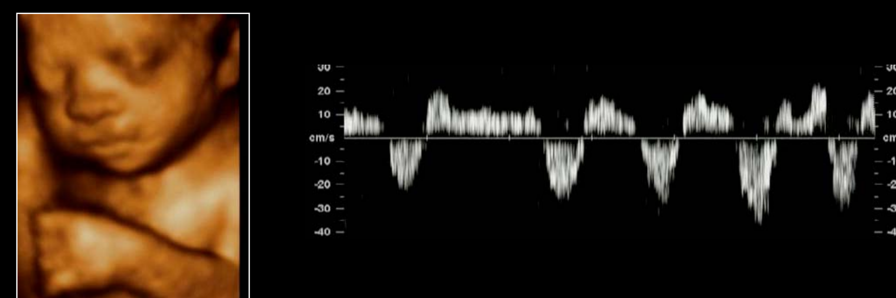
Saccular (26-term)/Alveolar (32+):

Alveoli develop from terminal saccules. Surface area increases. Capillary growth. Surfactant.

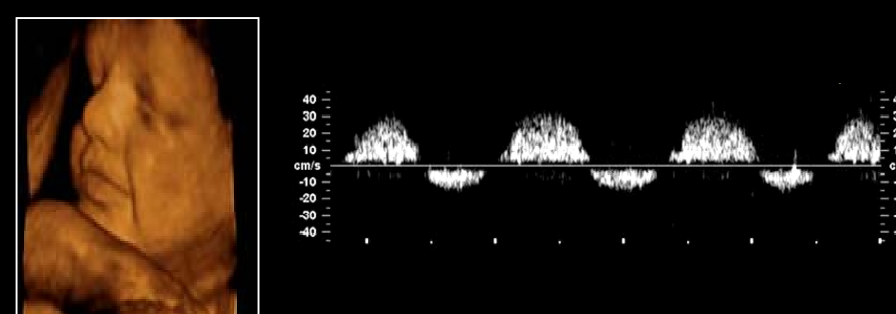
C4 : 28.0 - 31.6 w GA



C5 : 32.0 - 35.6 W GA

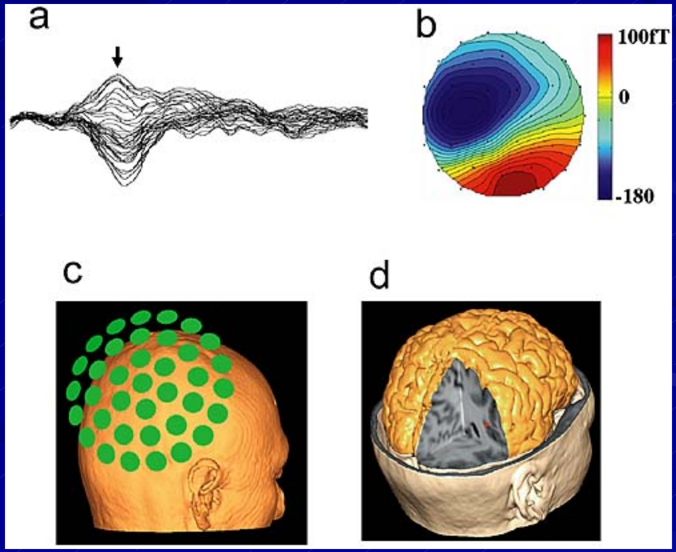


C6 : 36.0 - 39.6 w GA



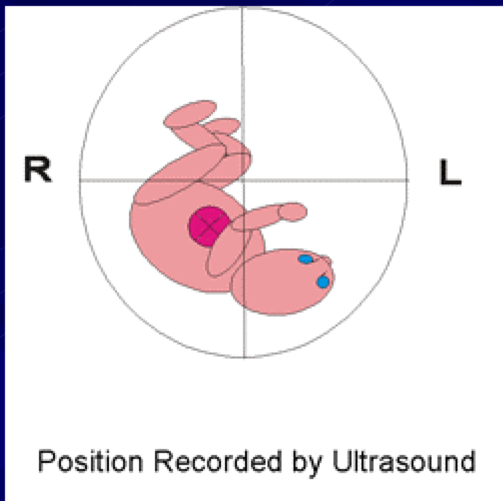
SQUIDs

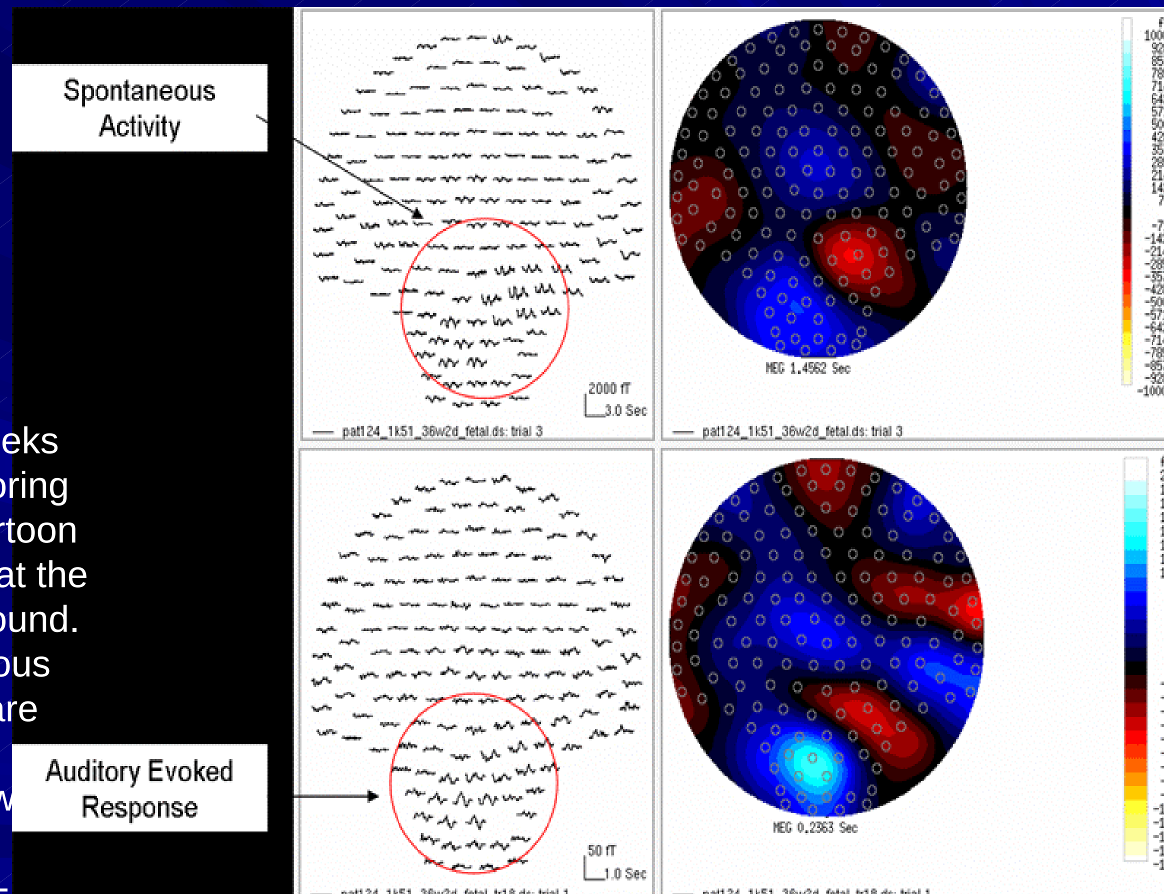
Superconducting
QUantum
Interference
Devices



Japan Information Processing
Development Center (JIPDEC)

Eswaran H, et al., Fetal magnetoencephalography—a multimodal approach. Developmental Brain Research 154: 57-62, 2005.
Preissl H, et al., Fetal magnetoencephalography: current progress and trends. Experimental Neurology 190: S28-S36, 2004.

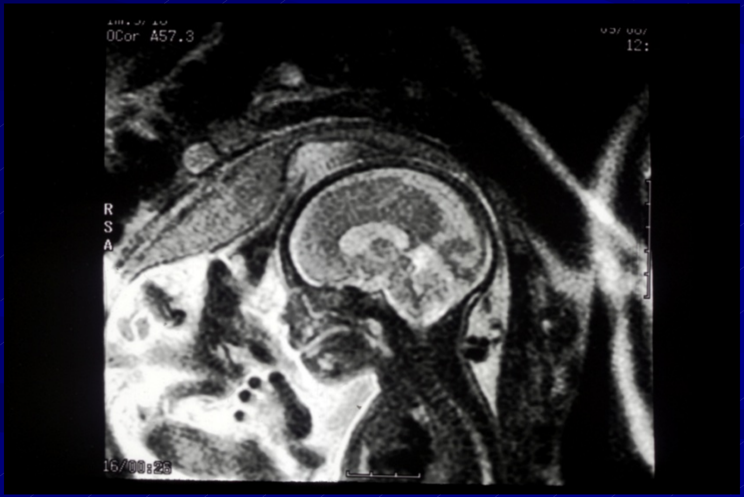


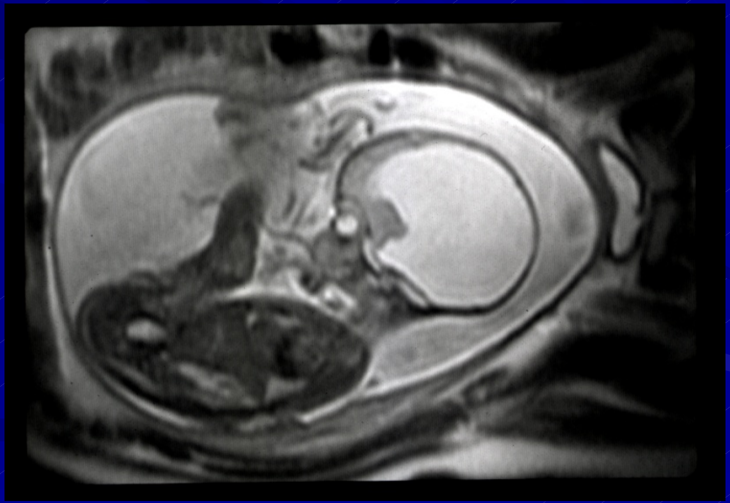


Researchers recorded a fetus at 36 weeks responding to sound stimuli and monitoring spontaneous brain activity. (Left): A cartoon indicates the intrauterine fetal position at the time of the study obtained using ultrasound. (Bottom left): The location of spontaneous brain activity and responses to sound are shown over SARA's 151 sensor array. (Bottom right): A color-coded map shows the magnetic field distribution for brain activity and sound response. The color-coding is based on the intensity and the direction of the magnetic fields at a given time point.

cortical auditory evoked responses (CAER)

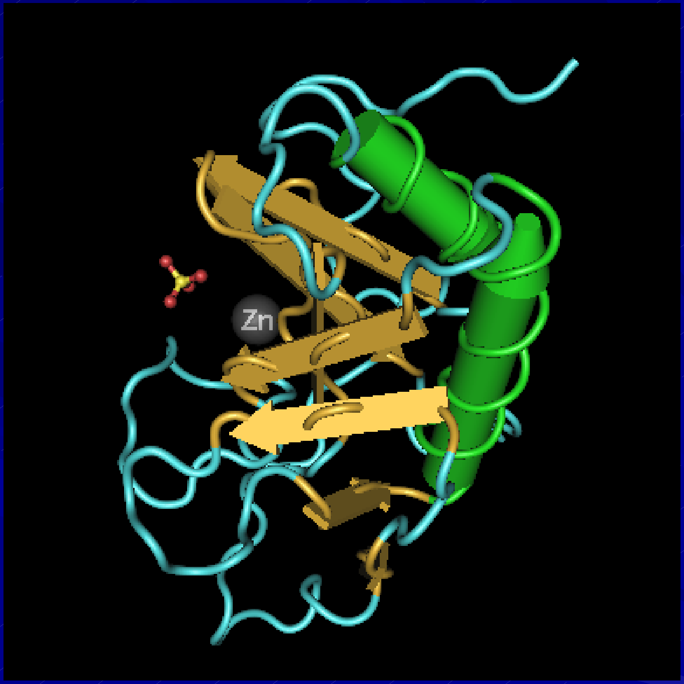
Fetal Magnetic Resonance





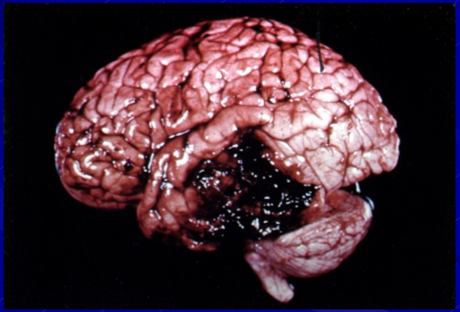
Linking Brain Maping, Genomics, Tissue Repair, and Fetal Brain Development

- Prime candidates for study are SHH and TGIF (Transforming Growth factor beta-Induced Factor)



Opportunities abound for…

- Multidisciplinary research teams using the right technologies for the benefits of fetuses, mothers, and the brain injured patient…
  - Neurologists/Neurosurgeons
  - Physiatrists/Therapists
  - Pathologists
  - Radiologists
  - Mathematicians
  - Geneticists
  - Software engineers
  - Perinatologists
- 2100 Severe TBI cases to date in OIF



www.urmc.rochester.edu/neuroslides/slide133.html

Toward Guidelines for Image-Guided Neurosurgeries

Jean-Jacques LEMAIRE MD, PhD
Inserm ERIM-ERI 14, Auvergne University
University Hospital of Clermont-Ferrand
France

Image Guided Neurosurgery & Guidelines

- 1983-2007

- 800 publications out of 860 (Removed: breast, prostate, nerve, body, liver, lung, pancreas, hepatic, colon, œsophage, pulmonary, block (anesth.), dog, baboon)

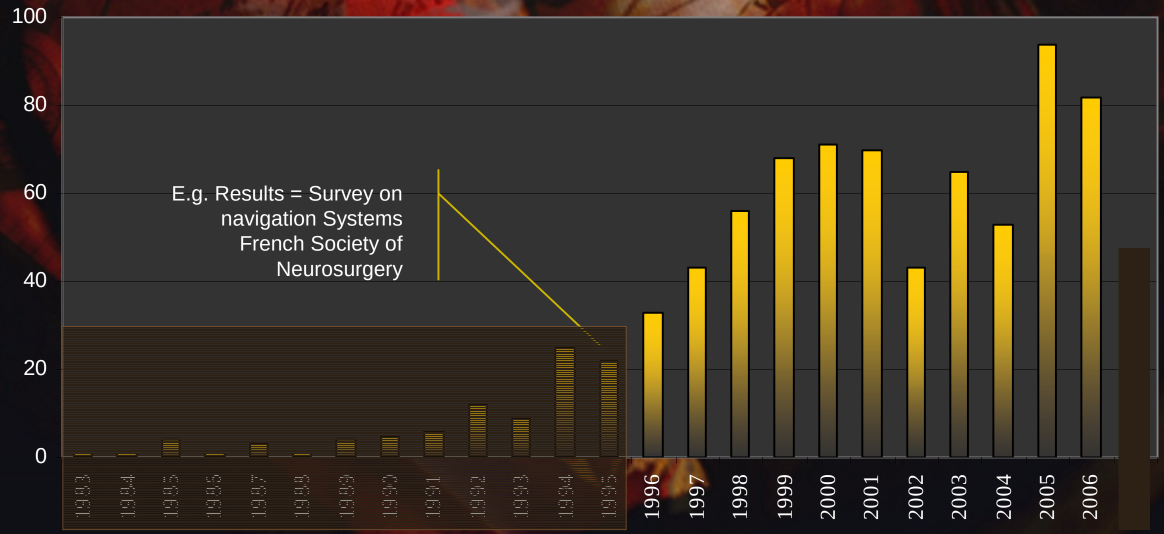
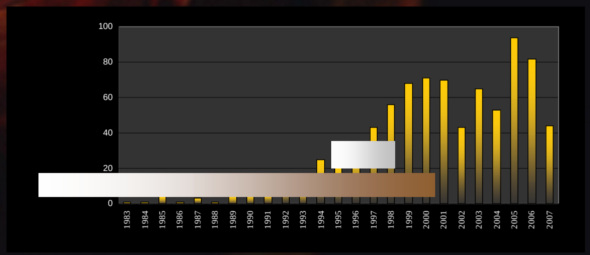


Image Guided Neurosurgery & Guidelines

control	21
quality	4
recommendations	1

Breeuwer M et al.
The EASI project--improving the effectiveness and quality of image-guided surgery
IEEE Trans Inf Technol Biomed 1998 Sep;2(3) 156-68

Lee JY et al.
Brain surgery with image guidance current recommendations based on a 20-year assessment
Stereotact Funct Neurosurg 2000;75(1) 35-48



The European Applications in Surgical Interventions (EASI) project

- image-guided neurosurgery
- for tumor resection, biopsy, endoscopy and catheter placement
- Philips Medical Systems (Nederland)

- Conclusion
  - *“The demonstrator is highly appreciated by the clinical users”*
  - *“And increase the accuracy of neurosurgery as well as the confidence of the neurosurgeon”*

From Neurosurgeries to Neuro Procedures

- 1 patient / a single act / invasive or not
- physical "tool"
    - Resection
    - Lesioning: coagulation, occlusion, freezing, ionization…
    - Non-lesioning modulation system (implant, external tool):
        - Stimulation (electric, magnetic), blockage system
        - Drug delivery system (pharmaceutical compound, graft…)
        - Multifunction system: e.g. electric membrane modulation + drug delivery
- physical route of administration :
    - http://www.fda.gov/cder/dsm/DRG/drg00301.htm: Interstitial, intracerebral, intralesional, intrameningeal, intra thecal, intraspinal, intratumor Intratissular …

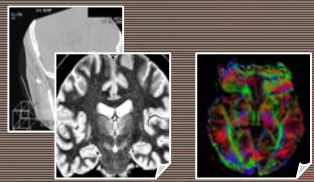
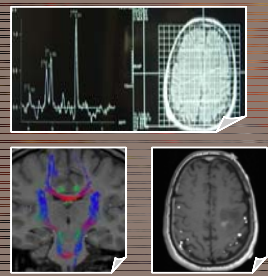
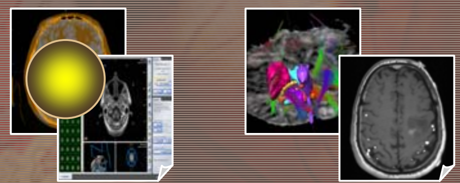
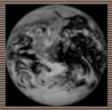
IGNP Current clinical context

- Procedures
  - Invasive
    - Neurosurgery: craniotomy, stereotaxy…
    - Endovascular interventional techniques
  - Non invasive
    - (r)TMS
    - radiosurgery [radiotherapy …GTV, PTV, PIV, TV]
- Core of IGNP: IDENTIFICATION (pre/intra)
  - Target
    - Anatomic structure
    - Lesion
  - Anatomic environment
    - Structures
    - Functions
- 3-STEP PROCESS
  - Imaging
  - Planning
  - Navigation

IGNP

Radiology

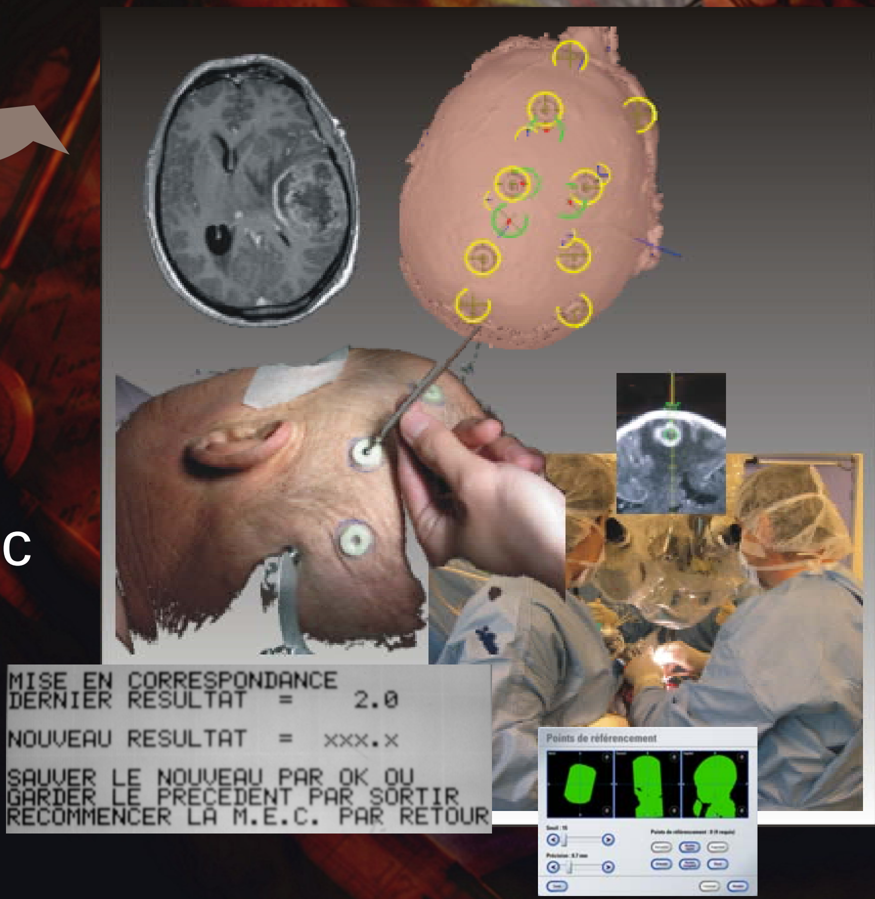
Procedure

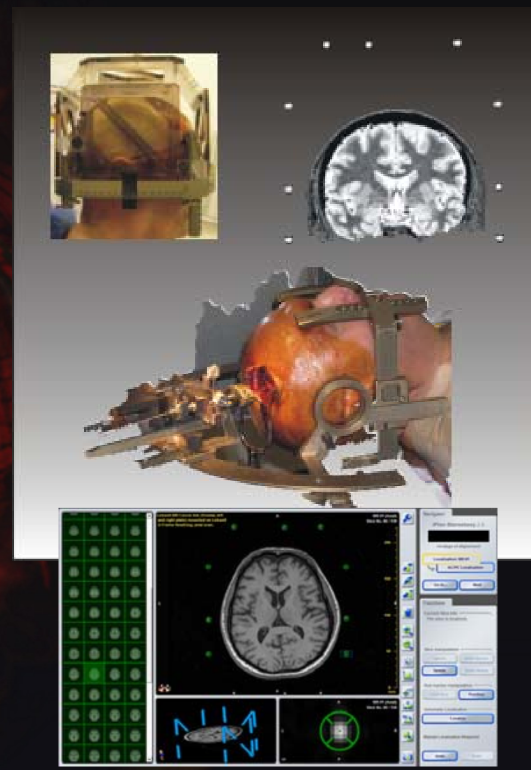
	Automatic	Semi Automatic	Manual
Imaging	 DICOM Digital Imaging and Communications in Medicine		Patient related: •head motion •patient's understanding Practitioner related •Injection of tracer
Planning	Pre planning processing: •Manufacturer-based •Dicom-based	Practitioner related: •Post imaging processing 	Practitioner related: •Medical knowledge: anatomy, pathology •User Interface utilization: objects, trajectories, data sets
Navigation	•Navigation •Matching	Practitioner related: •Imaging updating •Augmented reality 	Practitioner related: •Registration •User interface utilization

Information available in the clinical context:

Image-data matching

1.- With the **surgical space**: markers, stereotactic frame



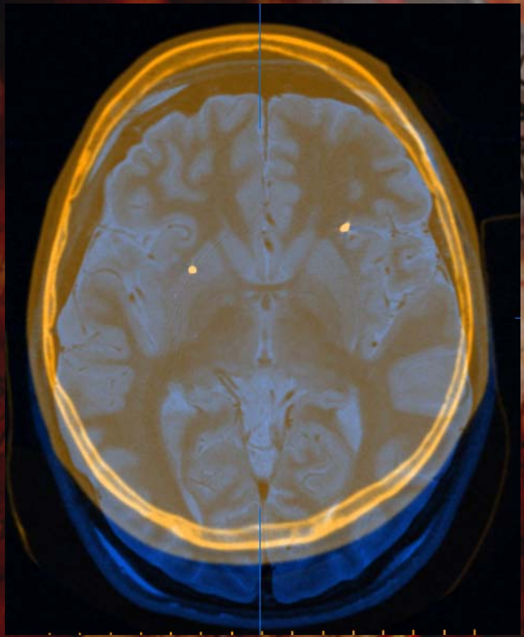


Information available in the clinical context:

Image-data matching

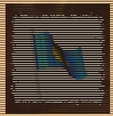
2.- Between **sets of images**

“Fusion”



Potentially useful parameters for the clinician

IGNP



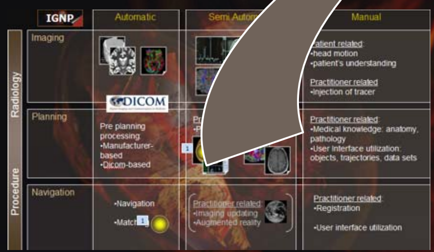
•Movements: detection / correction
•Data: Reconstructed or raw
•Voxel size, slice gap
•Location system: declaration, type…
•Post imaging processing: declaration, type

Imaging related parameters

- Intrinsic to the machine, CT, MRI, PET..
- Patient related (cooperation…)
- Imaging: resolution, type of sequence, raw or reconstructed data…
- Type of location system (stereotactic system, markers …)

Potentially Useful parameters for the clinician

IGNP



<u>Planning related parameters</u>

- Intrinsic to software
  - Pre processing => Dicom or not Dicom based)
  - Display modalities
- Operator related
  - Medical knowledge: anatomy, pathology
  - User Interface: creation of objects (volume, trajectories), data sets manipulation…

•Pre processing type
•Display parameters: voxel, interpolation
•UI processing: Object vs image-sets, matching settings

Potentially Useful parameters for the clinician

IGNP

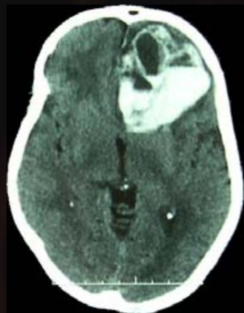
Navigation related parameters

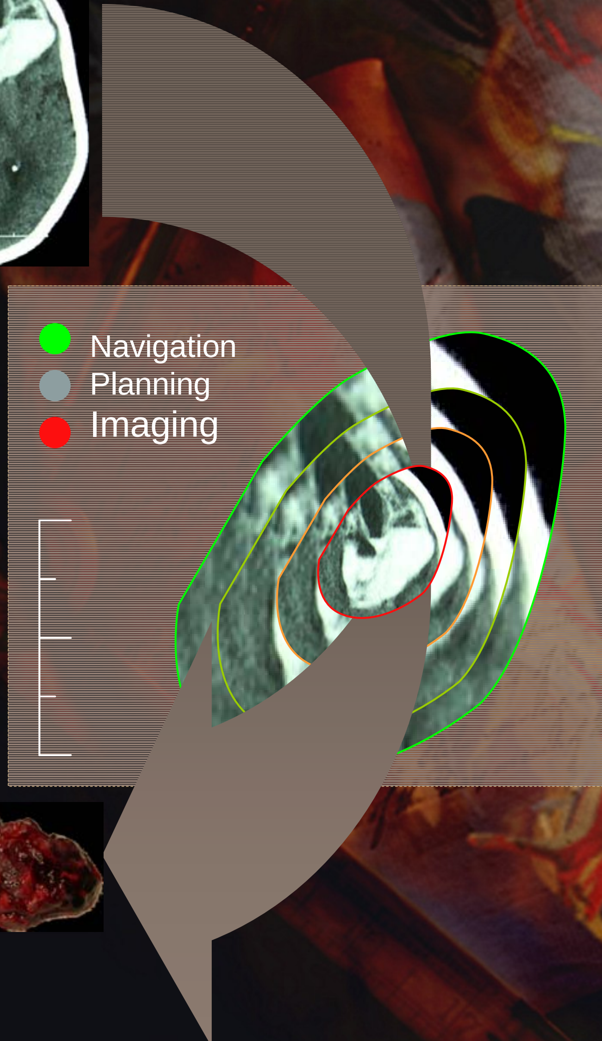
- Intrinsic to the technology
  - software
  - hardware
- Operator related
  - Registration quality
  - User interface utilization
- Accuracy of matching
  - Between the virtual and surgical spaces
  - Inside the virtual space (MRI, CT, Pet…)

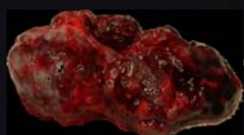
•Accuracy of matching (mm…)
•Display of
•Flags
•Confidence in objects

Concept

IGNP







- Validate
- Not validate
- Incomplete

Confidence step 3 = Imaging parameters

Confidence step 2= Planning parameters

Confidence step 1= Navigation parameters

Confidence step 0= **Object-Image**
Object=Target (T-I) or Neighbors (N-I)

Offer

- A meeting under the auspice of IBMISPS
  - Industry partners: Imaging, planning, navigation (Isis, Medtronic, BrainLab…)
  - Advanced user clinicians
  - Scientific societies: Bioengineering, Dicom, Neurosurgery…
  - Official governmental partners, …

- Toward guidelines
  - for the technologies
    - Pertinent parameters
    - Input-Output data format (object…)
    - Standard bench-tests; phantoms
  - for the practitioner
    - Medical education
    - Clinical practice

To anticipate the future clinical applications

- True stereoscopic 3D environments
  - learning: (augmented) virtual reality
  - practice:
    - augmented reality
    - enrichment of image-data => data fusion
- To mark out the route of mini-nano technologies

U.S. ARMY MEDICAL RESEARCH & MATERIEL COMMAND

IBMISPS 2007

Neuroscience Research at the U.S. Army Telemedicine and Advanced Technology Research Center: Opportunities for Engaging the Brain Mapping and Intraoperative Surgical Planning Communities

Kenneth C. Curley, MD

Kenneth C. Curley, MD

Chief Scientist, Neuroscience Portfolio Manager, TATRC
Assistant Professor of Military and Emergency Medicine, Surgery and Biomedical Informatics
Uniformed Services University of the Health Sciences,
Special Assistant to the Director, USUHS Center for Disaster and Humanitarian Assistance Medicine

COL Karl E. Friedl, Ph.D.
Director, TATRC
Fort Detrick, Maryland

COL Ron K. Poropatich, M.D.
Deputy Director, TATRC
Fort Detrick, Maryland

Disclaimer

The views expressed in this presentation are those of the presenter and do not necessarily reflect the official policy or position of the U.S. Army, the Department of Defense or the U.S. Government.

TATRC

Mission

Execute a congressional special interest program of medical science and technology research that maximizes benefits to military medicine

Vision

Be the model of government enablement of technology transfer to use

Research Portfolios

Key Product Lines

- Medical Robotics (Dr. Gilbert)
- Health Information Technologies (LTC Pak)
- Medical Imaging Technologies (Macedonia/ Marchessault)
- Advanced Prosthetics and Human Performance (Evans/Turner/ Lenhart)
- Computational Biology
  - BHSAI BIC (Reifman)
- Mobile Computing and Remote Monitoring (Lai)
- Simulation and Training Technology (Wiehagen)

New Initiatives & Basic Science

- Chronic Disease Management (Poropatich)
- Neuroscience (Curley/Cardin)
- Regenerative Medicine (Lai/Curley)
- Nano-Medicine and Biomaterials (Grundfest)
- Medical Logistics (Story)

TATRC

Funding Mechanisms

- Congressional Appropriation

  TATRC manages projects spanning basic principles of neurotrauma to clinical outcomes research. Many of these projects cross portfolios, engaging advanced imaging, modeling and simulation and prosthetics/human performance related technologies.

- SBIR and STTR Research

  TATRC manages several Small Business based initiatives focused on neuroscience. These include part task trainers for management of intracranial hemorrhage, trainers for regional anesthesia pain management and development of non-invasive systems for assessment of intracranial pressure.

- Research Partners (Innovation Funding)

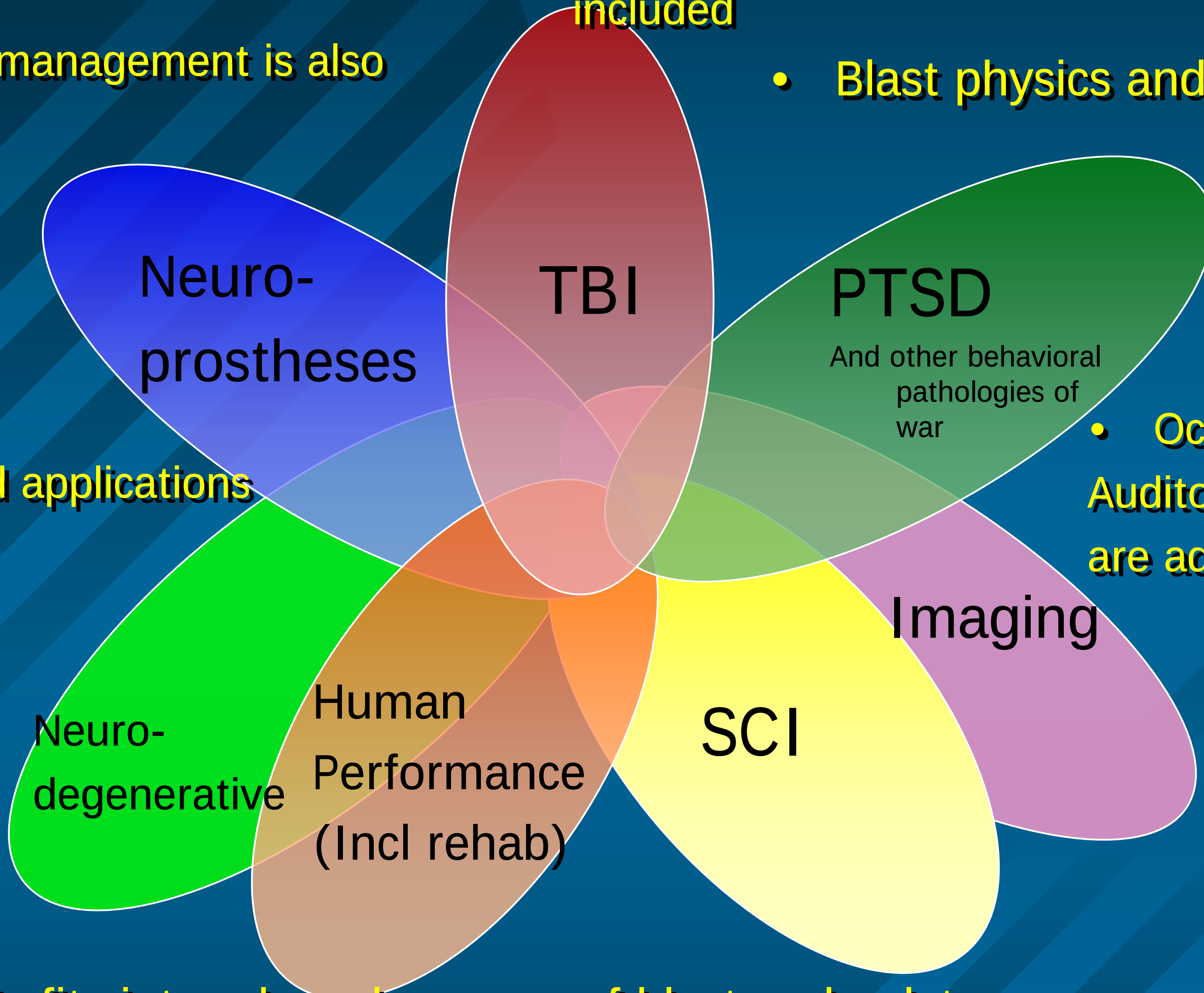
  TATRC has developed a large network of like-minded and engaged organizations and works to maintain synchronization within that network. Innovation funding is directed towards seed funding of new ideas of military medical relevance, and is limited to $250,000 (or less) per project.

History of the Portfolio

- Essentially two projects until FY06
  – Brain, Biology and Machine (Univ. Oregon)
  – Hyperbaric Oxygen Therapy for Cerebral Palsy
- With incidence of amputations, TBI and SCI came additional CSI funding. Also integrated management of RAD2 and RAD3 CSI projects.
- Neuroscience crosses many other TATRC portfolios, thus innovation funding was expended for
  – Neuroprosthetics (Vision)
  – Diagnostic Imaging (DTI)

A View of the Portfolio

- Education and training components included
- Pain management is also included
- Blast physics and monitoring included



- Ocular and Auditory issues are addressed
- Telemed applications
- This fits into a broader arena of blast and polytrauma as well

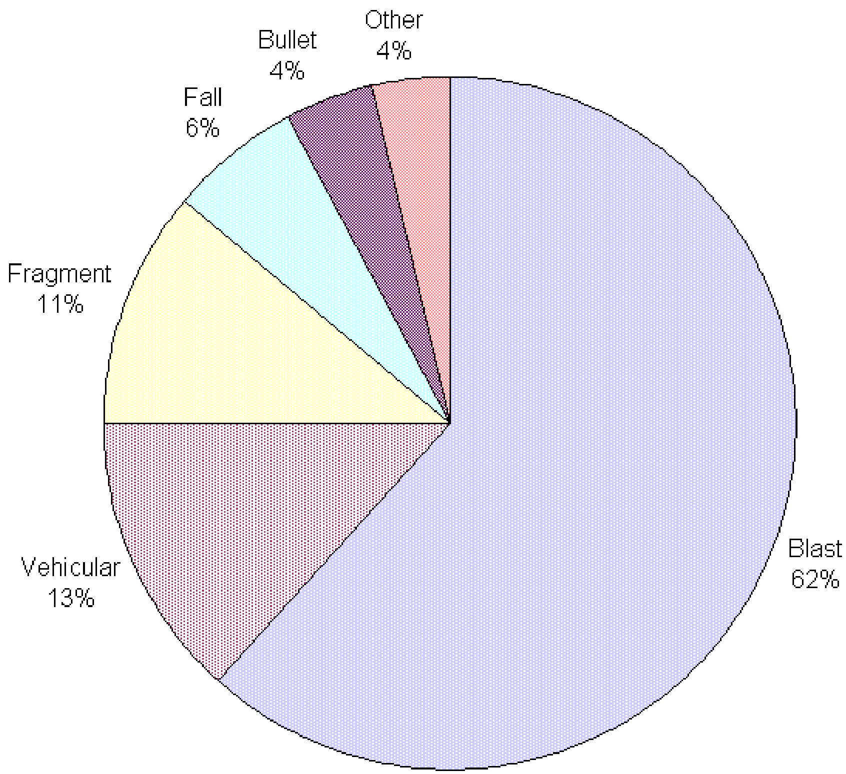
TBI Scope

- 1.4M incidents of TBI in the US annually
  – 235,000 hospitalized
  – 50,000 die
  – Cost to society is huge ($B's), both medically and financially
- Global War on Terrorism
  – >2,229 patients with TBI. Data from 1/03 - 04/30/07
  – Mild TBI (mTBI) remains a diagnostic challenge
  – Significant co-incidence of behavioral pathologies including PTSD
  – Post blast vasospasm is a novel phenomenon.

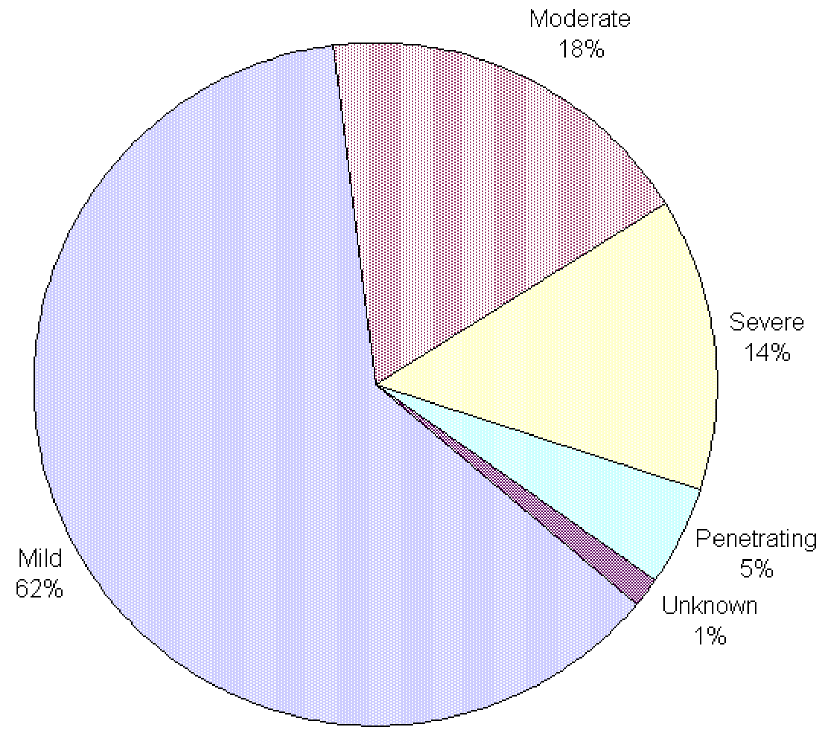
TRAUMATIC BRAIN INJURY-Scope of the Problem

Data from Defense Veterans Brain Injury Center (DVBIC) April 2006

TBI INJURY MECHANISM



TBI SEVERITY OF INJURY

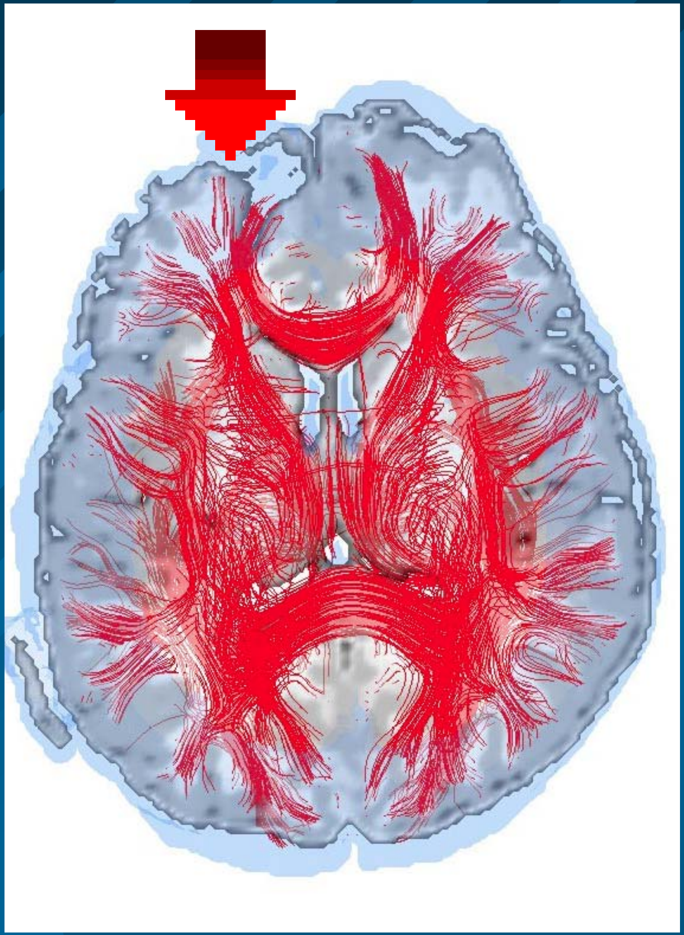


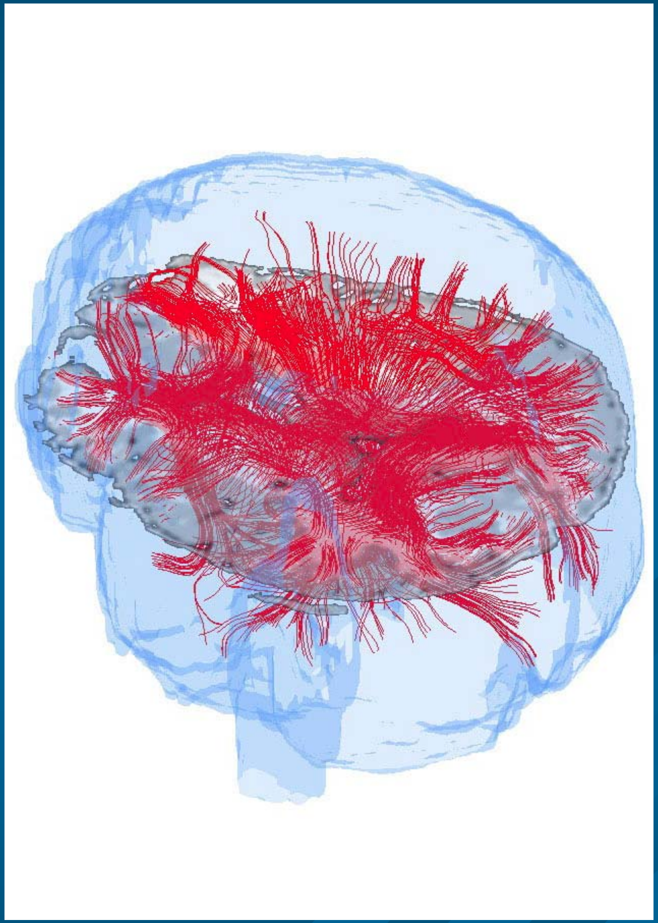
Spectrum of TBI range from Mild to Severe		
	Mild	62%
Operational Breakout:		
	OIF	96%
	OEF	4%

Source: Defense Veterans Brain Injury Center
POC: Colonel Michael J. Carino, OTSG

MRI-DTI Tractography to Quantify Brain Connectivity in Traumatic Brain Injury (Manbir Singh, PhD, USC)

Develop improved algorithms to address challenges in existing DTI technology (e.g. fiber boundaries and fiber crossing)





Images courtesy of Dr. Singh

Stimulation Through Simulation: Maintaining and Retraining Brain Organization Following Deafferenting Injuries.

Scott Frey, PhD, University of Oregon

Goal: Refine a computerized battery of motor simulation tasks to increase their effectiveness in stimulating sensory and motor systems of the human brain in the absence of volitional movement

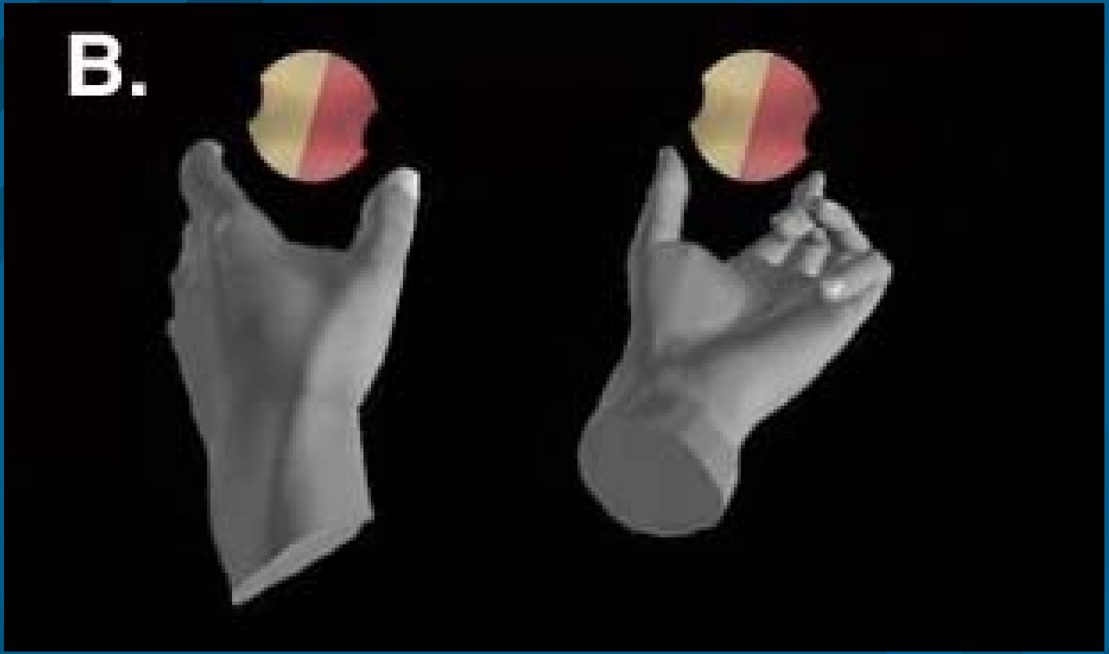


Image Courtesy of Scott Frey, PhD

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Grasping

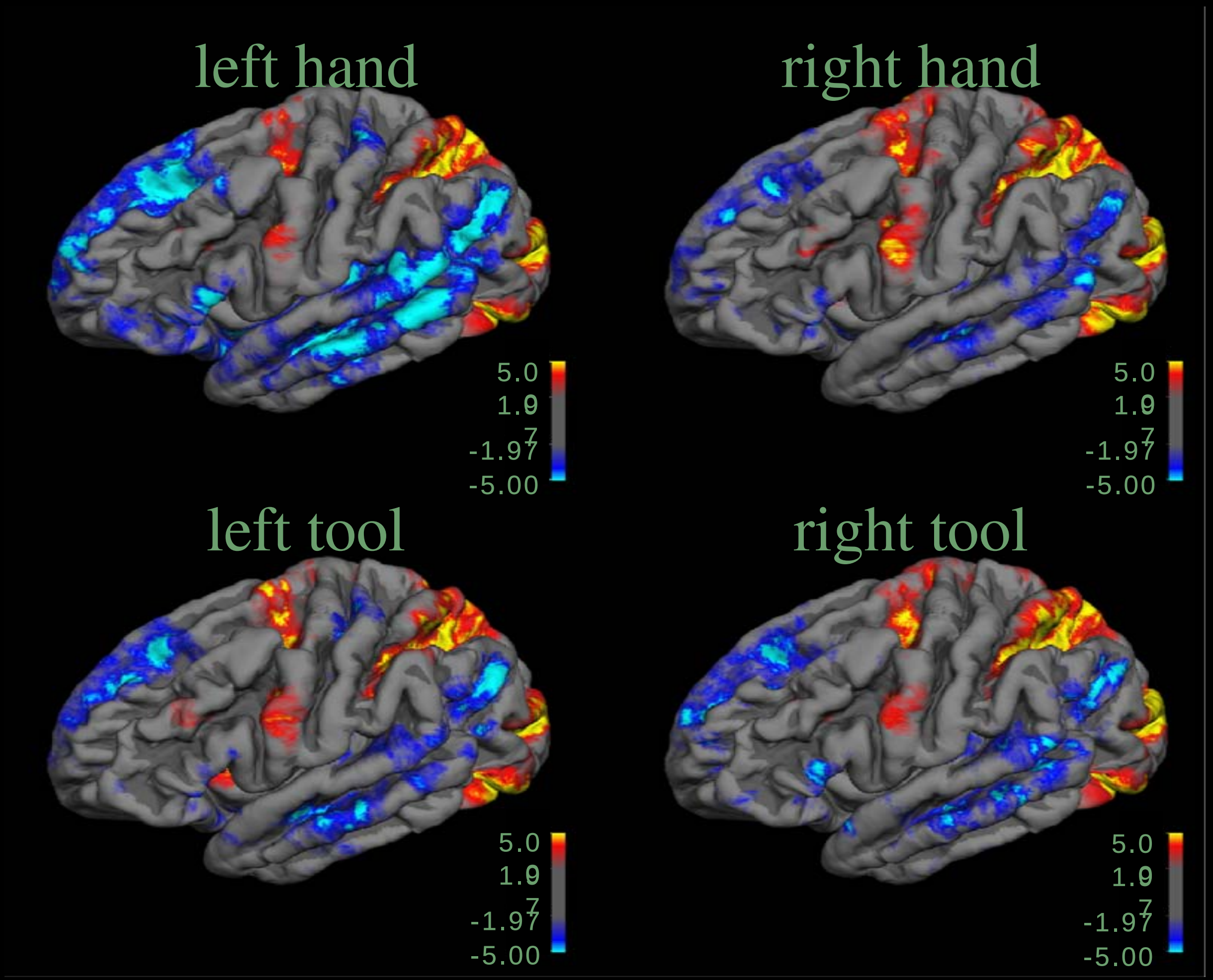
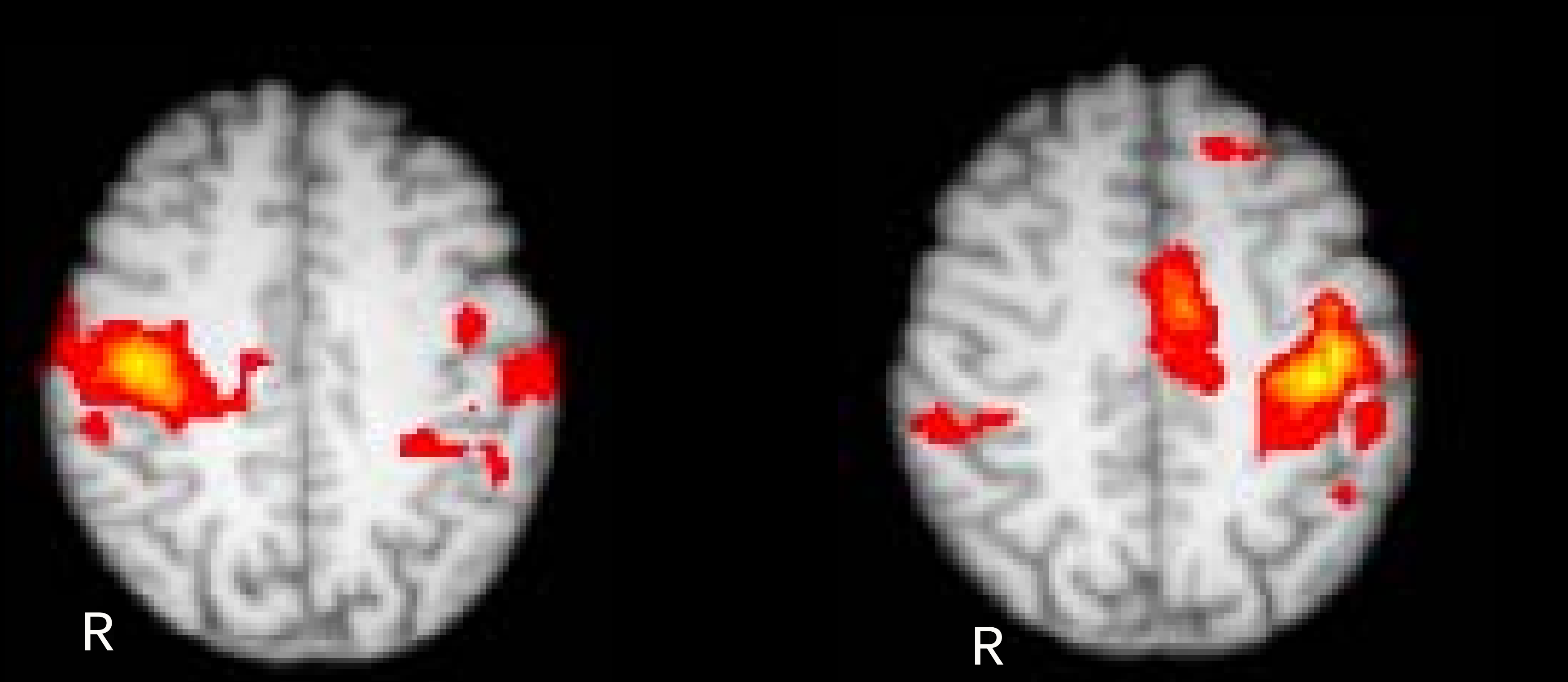


Image Courtesy of Scott Frey, PhD

4 mths. Post-op: Hand Movements



Intact Hand Transplanted Hand

Image Courtesy of Scott Frey, PhD

Portfolio Gaps

- Gaps-Protection/Prevention
  – Education (Providers and Servicemembers)
  – Outcomes/long term
    - Baseline assessments (from first provider to years after- opportunities for advanced imaging modalities)
    - EMRs/Databases
  – Personal Protective Equipment
    - Including dosimeters and physiologic monitors (blood based and image based biomarkers)
  – Nutrition (neuroprotection)
  – Pharmacology (neuroprotection/neuroprophylaxis)

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Portfolio Gaps

- Gaps-Diagnosis
  - Basic neurophysiology & pathology of mild to severe TBI
    - Blast effects (? RF, ultra/infrasound etc)
    - Models (*in vitro*, animal, human, computational)
    - Long-term effects
  - Real-time monitoring
    - Record the event-dosimeter (some work ongoing)
  - Imaging
    - Field-portable systems
    - DTI, fMRI, Susceptibility imaging
    - New modalities to allow imaging of patients with metal fragments etc
  - Biomarkers
    - Acute and chronic (work ongoing)
  - Assessment tools
    - Automated Neuropsychological Assessment Metrics (ANAM), etc need to be shorter, accurate
    - Need organic measures

TATRC

Portfolio Gaps

- Gaps-Management
  - Neuroprotection strategies
    - Pharmacology
    - Fluid management
    - Physiologic parameters-optimal
  - Outcomes assessments
    - Impact of polytrauma
    - Assessment of hand-offs to next level of care/rehab
  - Monitoring (less invasive)
  - Imaging (functional and structural)
  - Regenerative medicine
  - Guidelines
    - Exist but based on little existing EBM

TATRC

Portfolio Gaps

- Gaps-Rehabilitation
  - Nutrition
  - Continued outcomes research
    - Databases/EMRs (continuity and interoperability)
    - Imaging-progression and prognostics
  - Neuroprosthetics
  - Neuromodulators
    - Imaging and surgical planning
  - Pharmacology
  - Long-term regenerative/molecular medicine
  - Re-training/education
    - Use of VR/simulation

TATRC

Questions?

Thank you!

Gliomas and Vessel Shape as Monitored by Magnetic Resonance Angiography (MRA)

Bullitt E, Van Dyke T, Reardon DA, Barboriak DP, Lin W

CASILab, University of North Carolina-CH and Preston Robert Tisch Brain Center at Duke

UNC CASILAB

Accidental Observation: Cancer Has Abnormal Vessel Tortuosity

Hypothesis: quantitative measures of vessel shape can assess tumor malignancy and evaluate response to treatment

UNC CASILAB

Background: Malignant Tumor Vessels

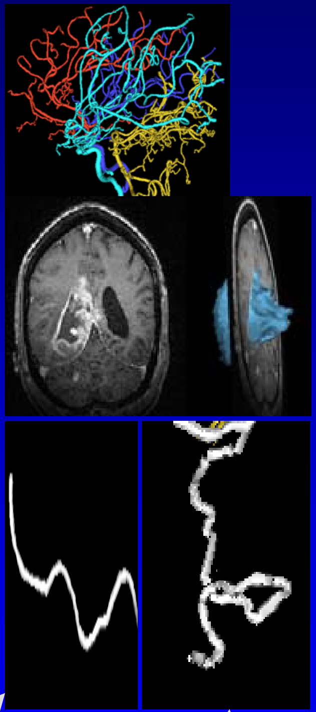
Li et al Initial stages of tumor cell-induced angiogenesis: evaluation via skin window chambers in rodent models. J Natl Cancer Inst 92:143-147, 2000. Images used with permission.

1) Abnormal vessel tortuosity precedes sprout formation (Li). Affects larger vessels passing through region. Shape abnormalities extend beyond tumor boundaries.
2) Successful tumor treatment normalizes vessel shape (Jain)
3) Abnormal vessel tortuosity may be N02 and VegF related (Folkman)

UNC CASILAB

Assessment of Cancer by Statistical Measures of Vessel Shape

1) Extract the vessels from MR
2) Define the tumor margins from MR
3) Measure vessel shapes and compare to healthy subjects: “Malignancy Probability”



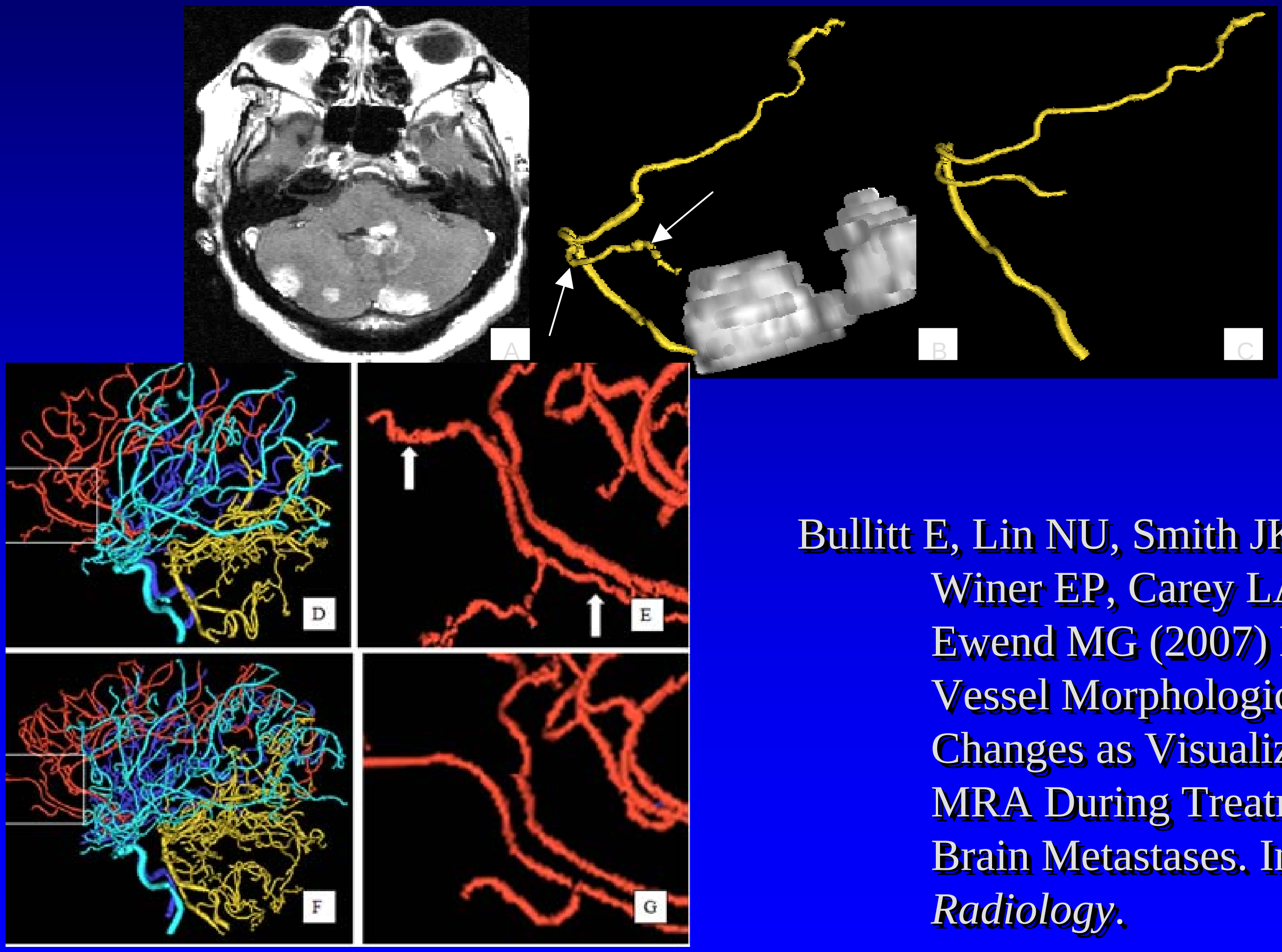
Healthy shape

Cancer

Bullitt E, Zeng D, Gerig G, Aylward S, Joshi S, Smith JK, Lin W, Ewend MG (2005) Vessel tortuosity and brain tumor malignancy: A blinded study. *Academic Radiology* 12:1232-1240.

UNC CASILAB

Normalization of Vessel Shape At Month 2 During Treatment



Bullitt E, Lin NU, Smith JK, Zeng D, Winer EP, Carey LA, Lin W, Ewend MG (2007) Blood Vessel Morphological Changes as Visualized by MRA During Treatment of Brain Metastases. In press *Radiology*.

UNC CASILAB

2 Ongoing Studies in Glioblastoma

1) Genetically engineered mouse model

2) Human studies: Glioblastoma treated with anti-angiogenic agents

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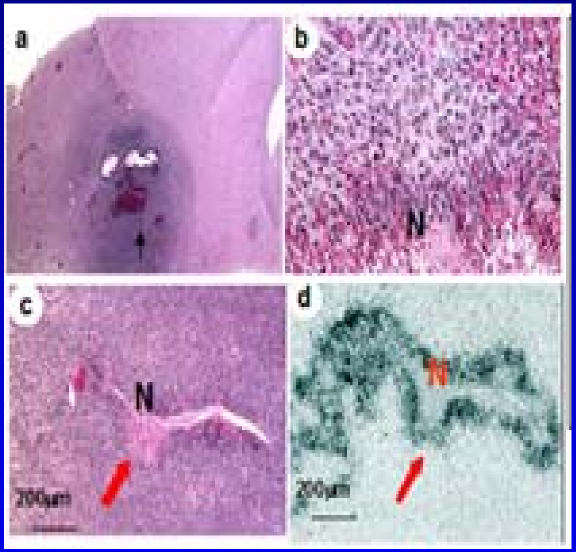
Mouse Glioblastoma Model (Van Dyke)

- pRb pathway aberration, activation of EGF receptors, inactivation of PTEN.
- IP injection of 4-OH-tamoxifen at 3 months.
- Fully penetrant model; animals moribund 8 mos

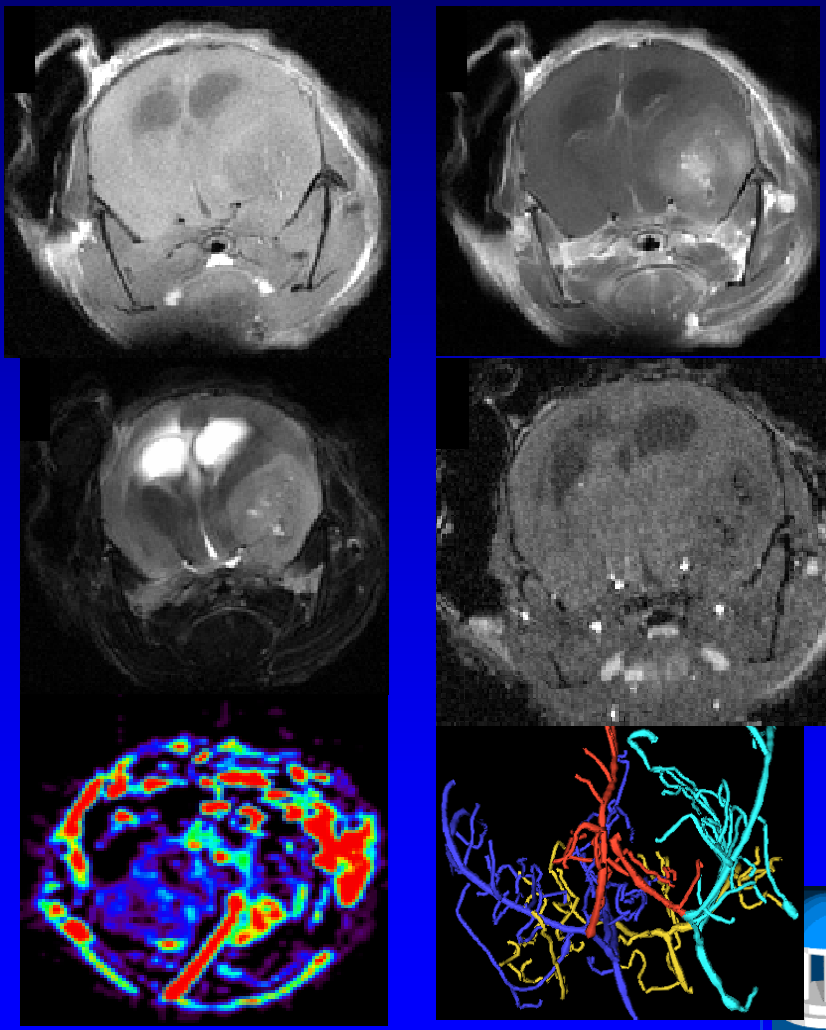


UNC CASILAB

Mouse Imaging by 3T MR

1) T1, T2, MRA, T1-GAD, perfusion (AMI-227)
2) MRA 100 x 100 x 100 microns

Bullitt E, Aylward SR, Van Dyke T, Lin W (2007) Computer-Assisted Measurement of Vessel Shape from 3T Magnetic Resonance Angiography of Mouse Brain. In press *Elsevier Methods*



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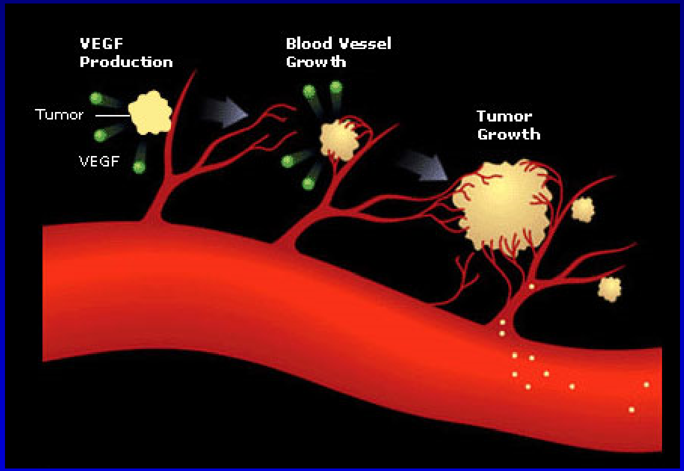
Questions to be Answered

1) Abnormalities of vessel shape mark tumor development and treatment response?
2) Relationship "macro" and "micro" vessel imaging?
3) Vessel wall changes by histology?



www.gene.com/.../oncology/angiogenesis.jsp

Mouse Glioma Imaging (In Progress)

1) 8 mice imaged with known GBM: MP 73-100% in 7 and 51% in one mouse with tumor not covered by MRA.
2) 1 mouse imaged without brain tumor: MP 13%.
3) 5 mice imaged sequentially beginning prior to tumor onset; MP appears to begin to rise weeks/months before gadolinium enhancement

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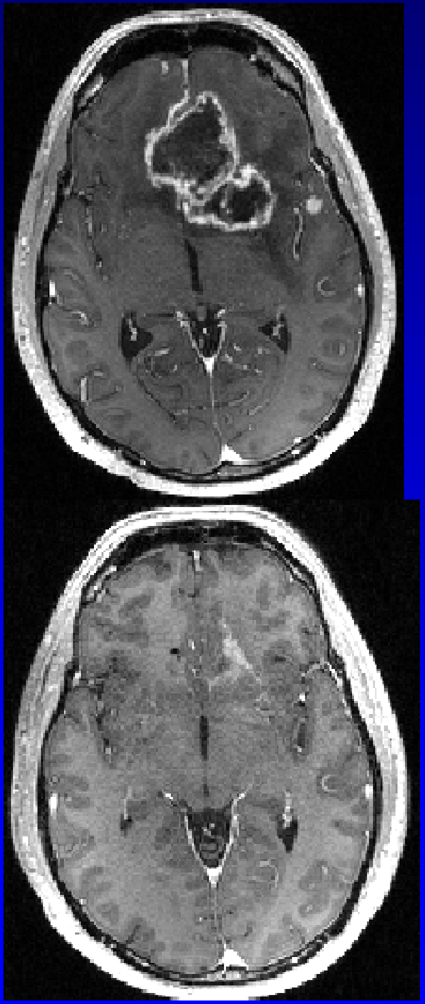
Imaging of Human GBM During Anti-Angiogenic Therapy

1) 18 patients who failed other treatment scanned sequentially during anti-angiogenic therapy (Avastin [anti-VEGF] + Tarceva [anti-EGFR] + other)
2) All patients exhibited reduction in tumor volume by T1-GAD
3) Some developed progressive neurological deficits and have died nevertheless.



UNC CASILAB

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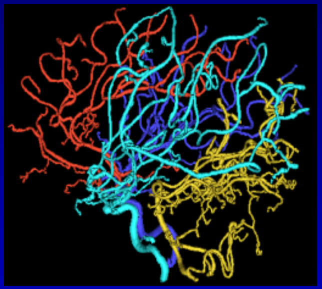
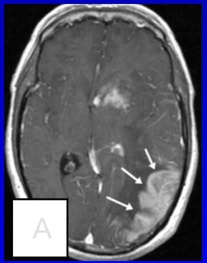
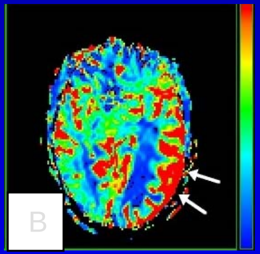






Bullitt E, Reardon DA, Smith JS (2007) A Review of Micro and Macro Vascular Analyses in the Assessment of Tumor-Associated Vasculature as Visualized by MR. *NeuroImage* 37 Supp 1: S116-S119 http://dx.doi.org/10.1016/j.neuroimage.2007.03.067

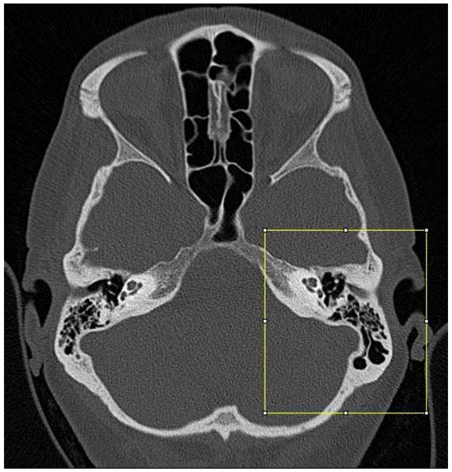
Vessel Shape During Anti-Angiogenic Treatment

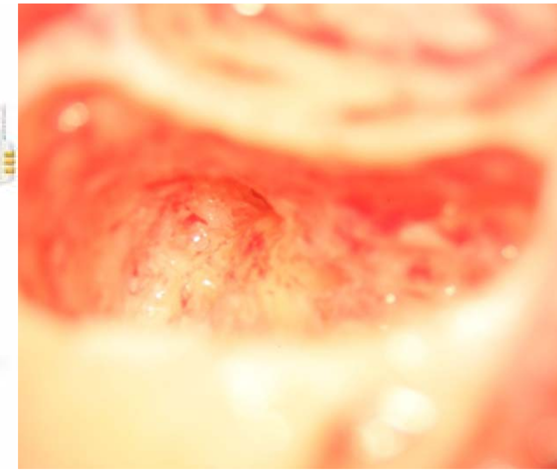
1) Vessel shape does not always normalize, despite reduction in GAD enhancement
2) Only a subset of patients exhibit vessel normalization
3) This study is in progress…

Acknowledgements

Supported by

- R01 EB00219 NIH-NIBIB
- R01 CA 124608 NIH-NCI
- Duke SPORE grant





Navigation Support through Preoperative Simulation of Cranial Interventions

Andreas Pommert[1], Karl Heinz Höhne[1], Andreas Petersik[1], Bernhard Pflesser[1], Ulf Tiede[1] , Boris Tolsdorff[2] , Max Heiland[3]

[1]VOXEL-MAN Group, [2]Dept. of Oto-, Rhino-, Laryngology, [3]Dept. of Oral and Maxillofacial Surgery
University Medical Center Hamburg-Eppendorf, Hamburg, Germany

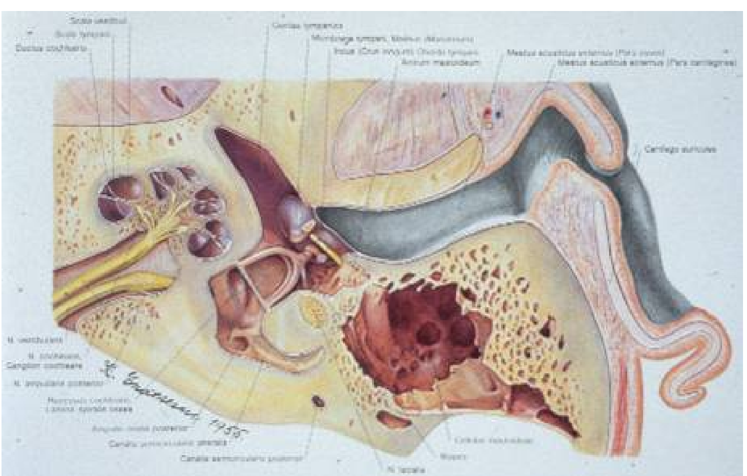
Cranial interventions in oto-rhino-laryngology …

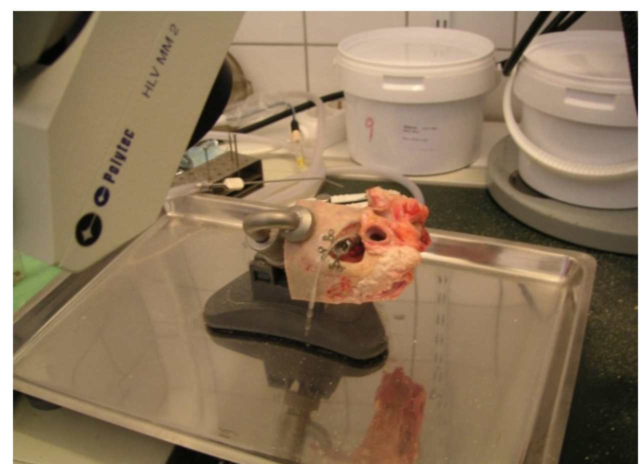
- temporal bone surgery
- endonasal sinus surgery
- …

- spatially complex
- high variability
- organs at risk
  - eyes
  - facial, optic, olfactory nerves
  - cranial base
  - sinuses
  - internal carotid arteries
  - …

Conventional training

- understanding of anatomy from textbooks and atlases
- training based on human specimens
  - limited availability
  - no pathologies
- training on the patient?





Aviation industry

www.lufthansa.com

Boeing 737-300 flight simulator

www.lufthansa.com

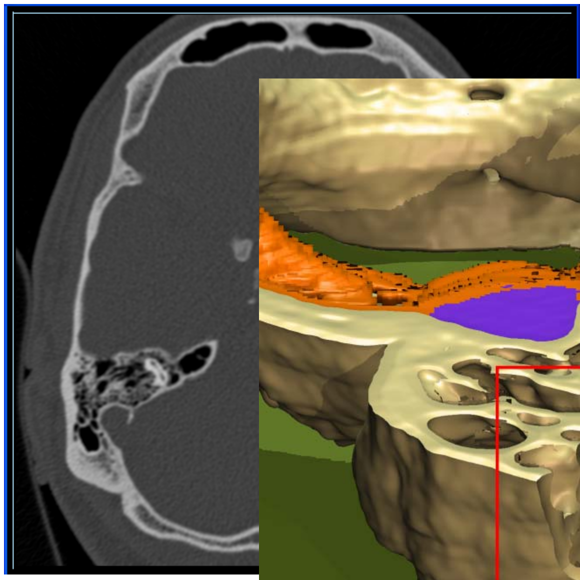
No pilot ever gets a license without extensive simulator training!

Goals

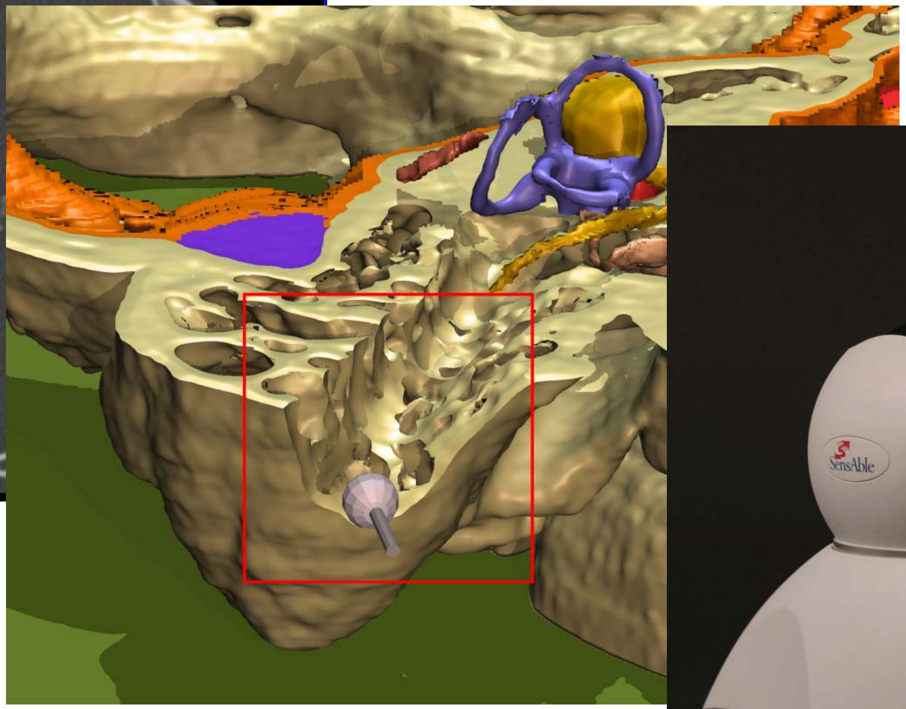
develop a surgery simulator for cranial procedures

- training
- preoperative surgery rehearsal
- intraoperative navigation support

Methods



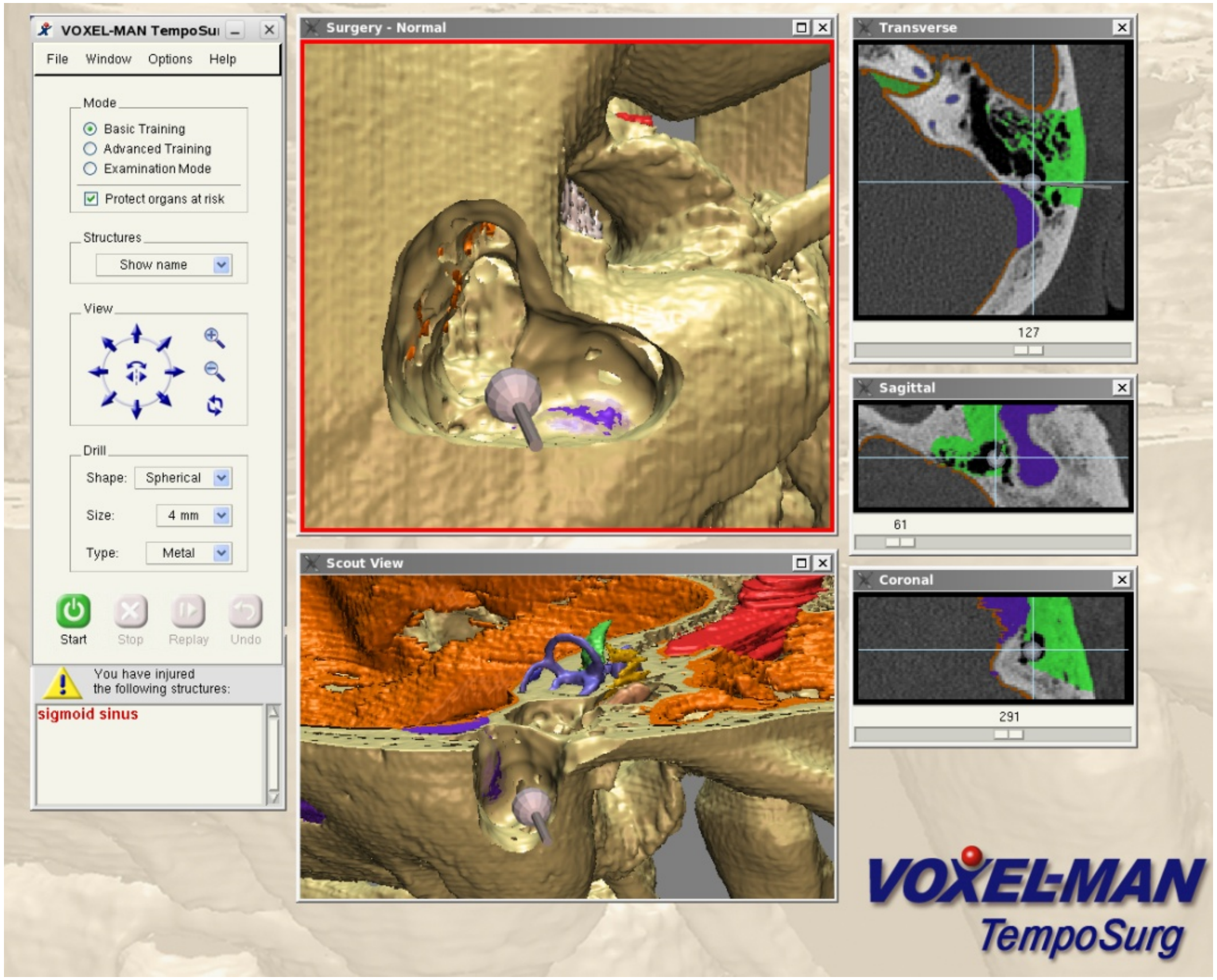
CT data



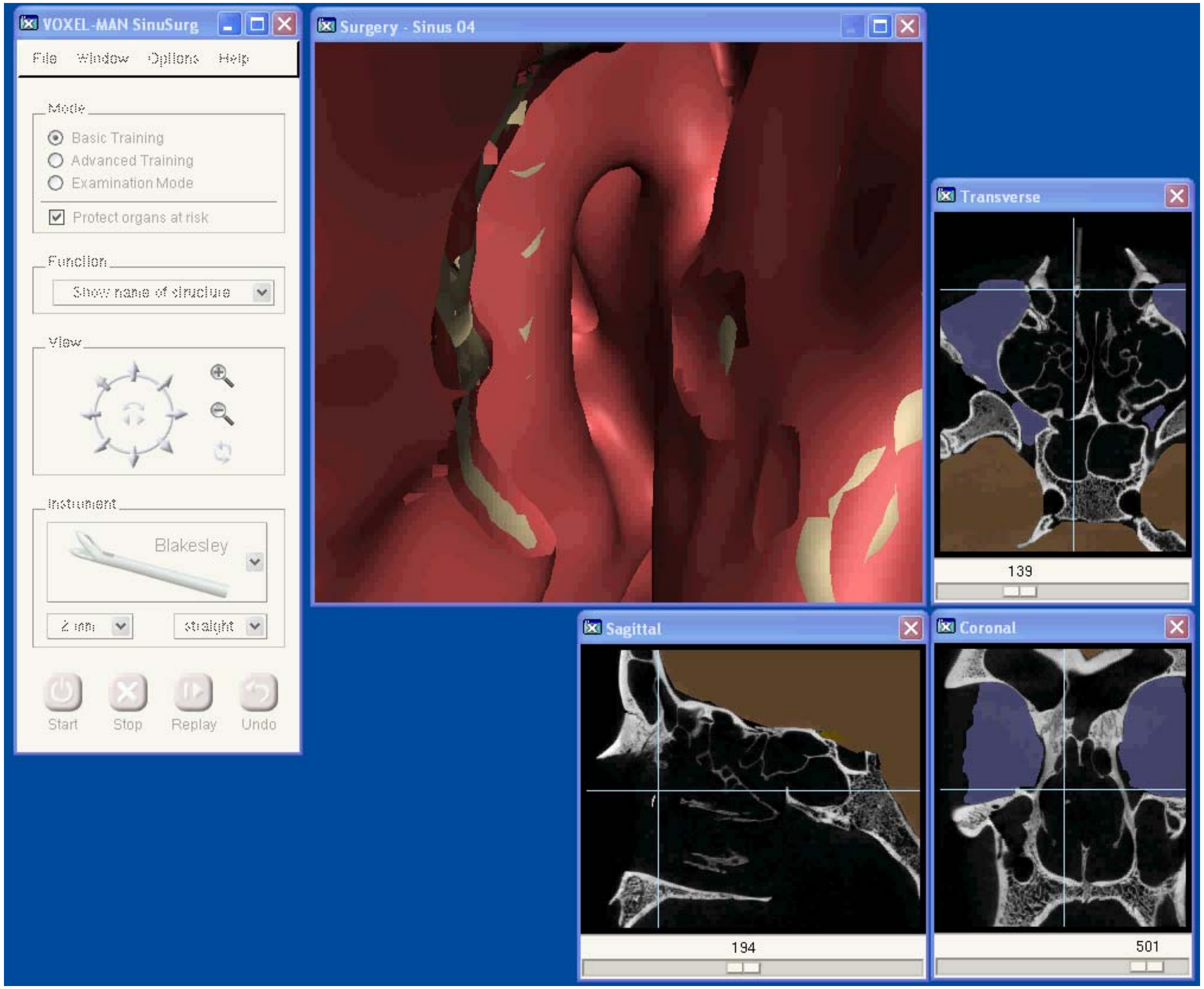
3D voxel models
visualization
manipulation

haptic rendering

Temporal bone surgery simulator



Endonasal sinus surgery simulator



Evaluation of VOXEL-MAN simulators

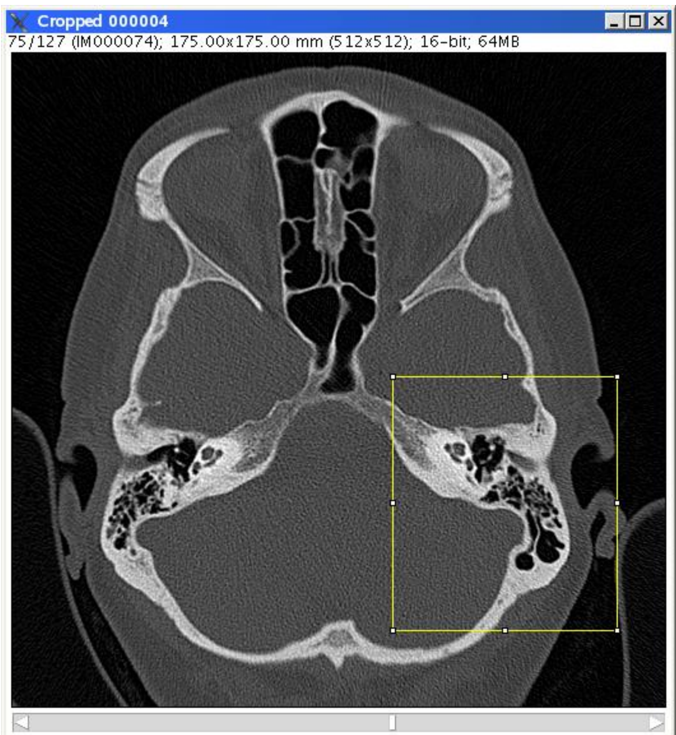
- Training with a virtual apicectomy simulator appears to be effective, and the skills acquired are transferable to physical reality.

  Sternberg et al., Int. J. Oral Maxillofac. Surg. 36 , 5 (2007), 386-390

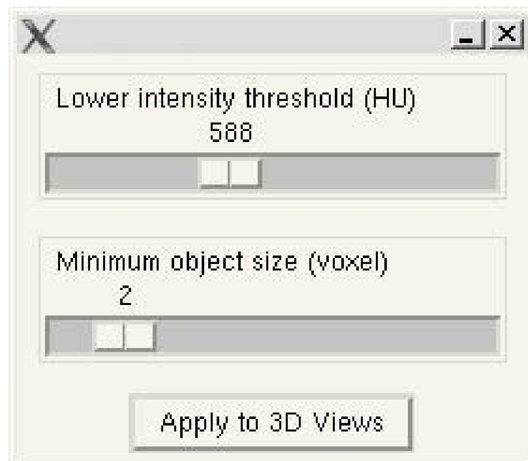
- This study suggests that otolaryngology trainees could accomplish initial temporal bone training on a VR TB simulator, which can provide feedback to the trainee, and may reduce the need for constant faculty supervision and evaluation.

  Zirkle et al., Laryngoscope 117, 2 (2007), 258-263

Creating patient specific models for rehearsal

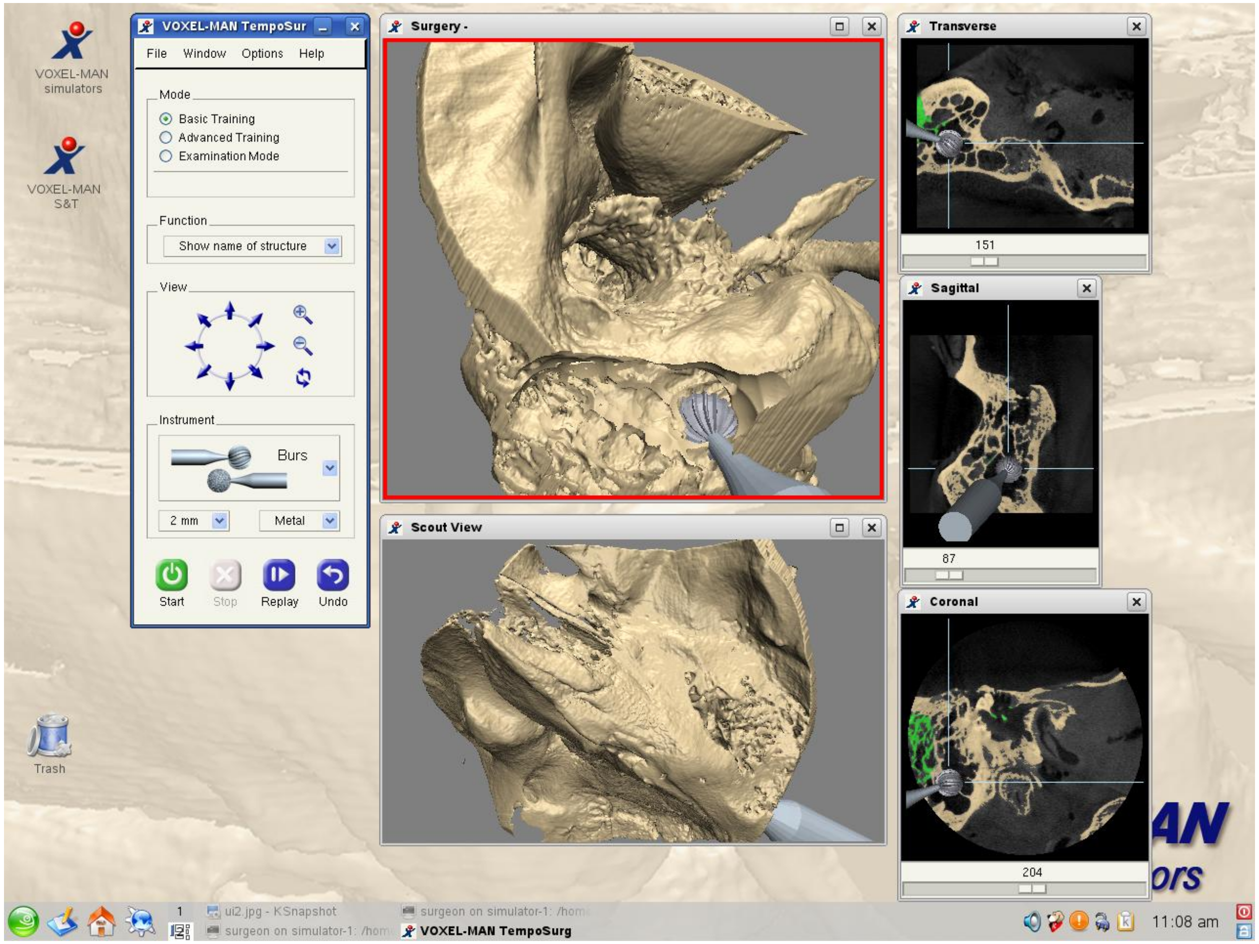


CT data



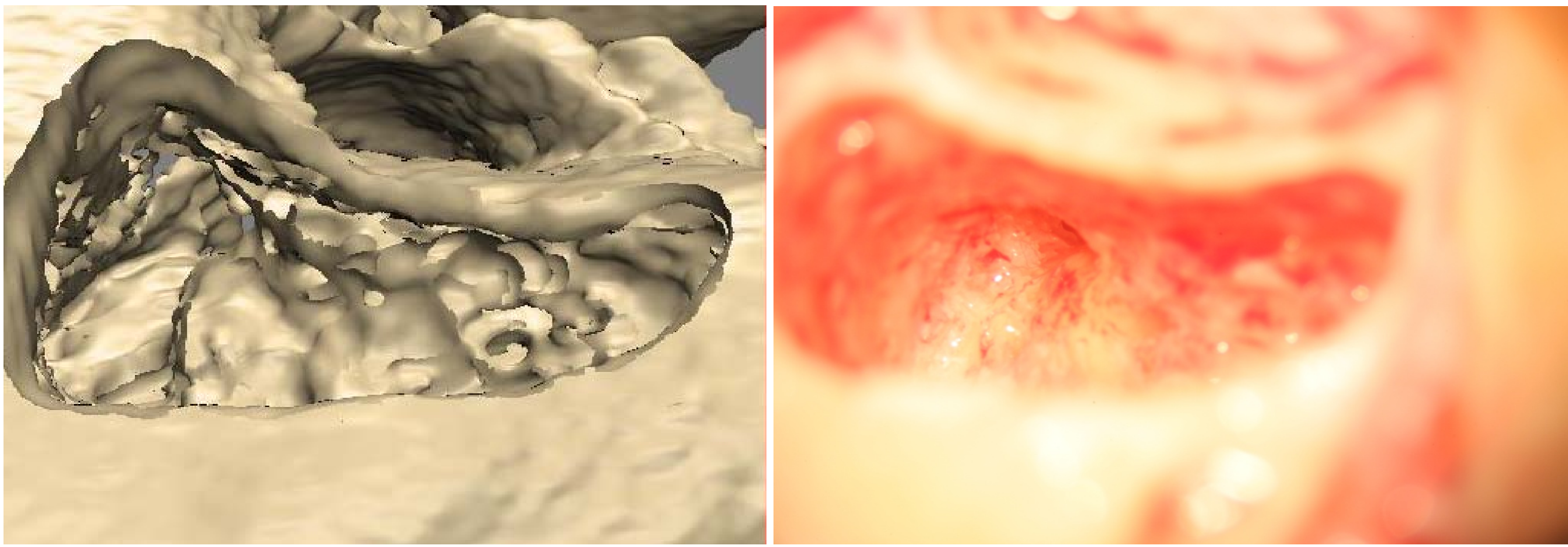
3D bone model

Surgery rehearsal



cone beam CT data courtesy of Carsten Dalchow, Dept. of ORL, Park-Klinik Weissensee, Berlin

Surgery rehearsal



preoperative saccotomy intraoperative

Why not use results of surgery rehearsal for intraoperative navigation support?

B. Tolsdorff et al., Int. J. Comp. Assist. Radiol. Surg. Suppl. 2007

Surgery navigation

www.brainlab.com

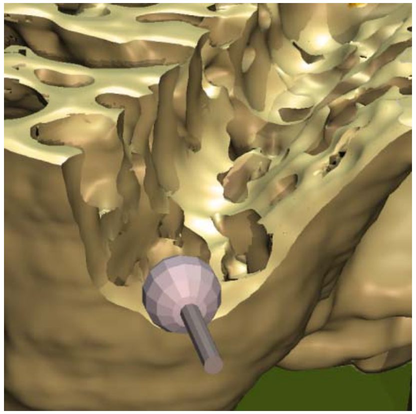
BrainLAB VectorVision

System connection

image data & coordinate systems

tool positions

corresponding
cross-sections and views

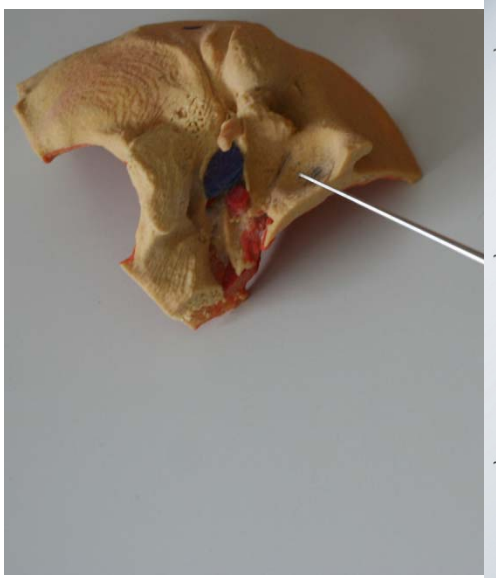


VectorVision
navigation system

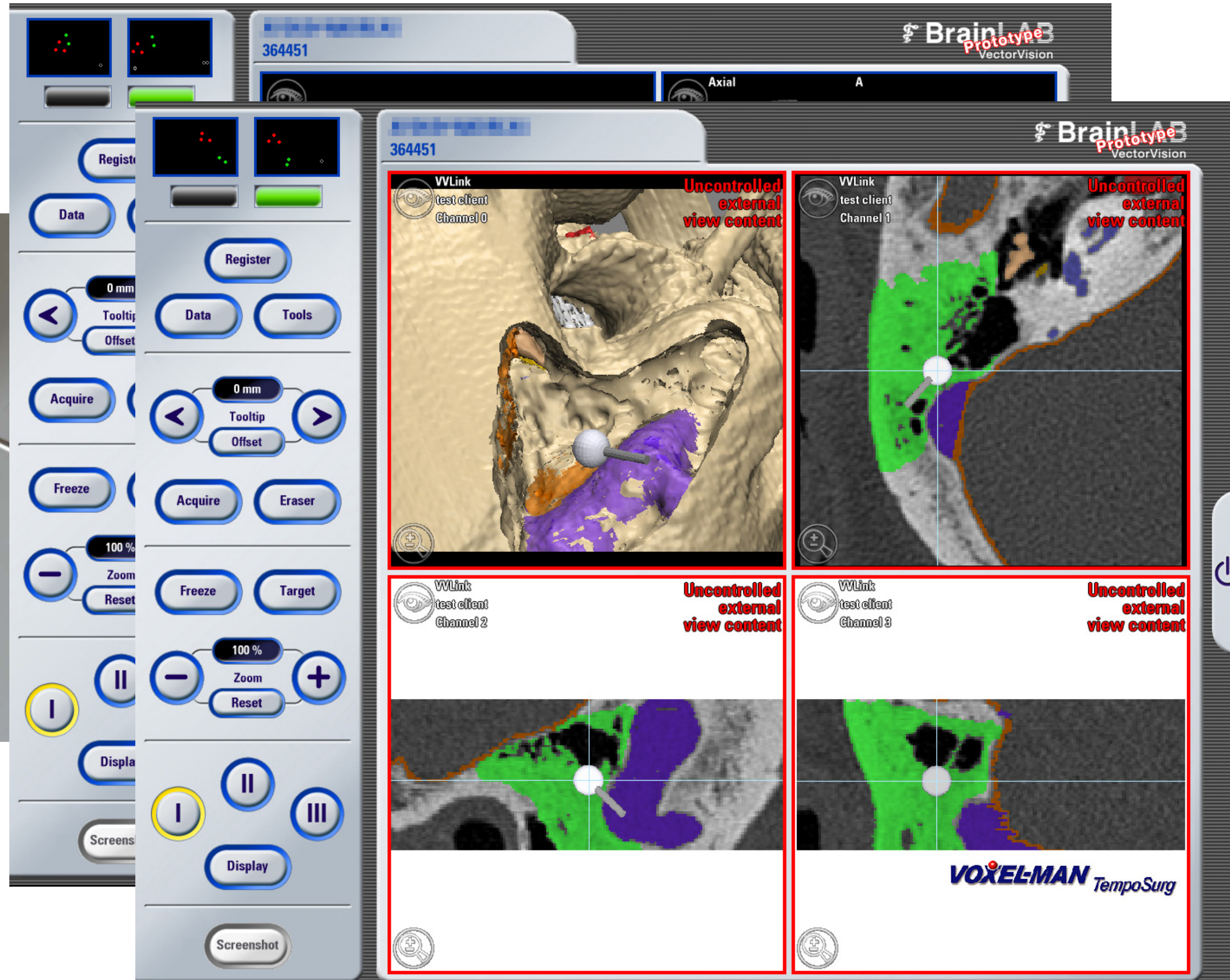
VectorVision Link
real-time client/server interface

VOXEL-MAN
surgery simulator

Prototype

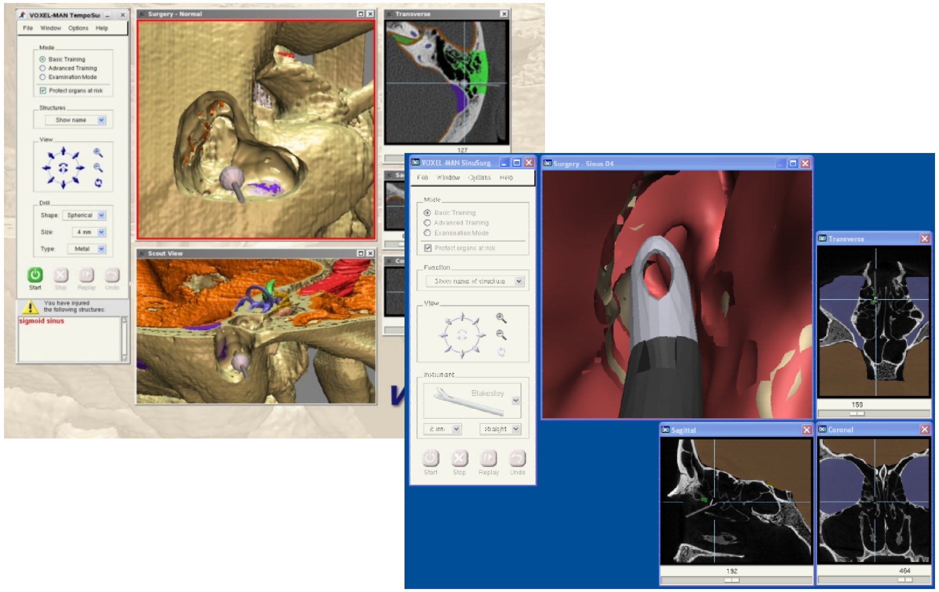


test setup



corresponding images from simulator

Conclusions



- surgery simulator
  - temporal bone surgery
  - endonasal sinus surgery
  - ...
- effective as a training tool
- promising for surgery rehearsal for difficult cases
  - workflow
  - radiation exposure
- connection to surgery navigation system
  - intraoperative access to preoperative results
  - alarm function

UF UNIVERSITY of FLORIDA | Tissue Biomechanics Laboratory

Determination of Macromolecular Concentration Following Direct Infusion into Hydrogel using Contrast-Enhanced MRI

Jung Hwan Kim[1], Thomas H. Mareci[2], and Malisa Sarntinoranont[1]

[1]Department of Mechanical & Aerospace Engineering
[2]Department of Biochemistry and Molecular Biology
University of Florida

Convection-Enhanced Delivery (CED)

- Infuse therapeutic agents directly into brain tissue
- Enhance macromolecular transport
- Bypass the blood-brain barrier
- Reduce systemic toxicity
- Reproducible and clinically safe

Chen et al. 1999, J. Neurosurg.

How to monitor or predict drug distribution?

Features of the Transport Model

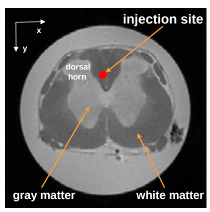
Heterogeneity of tissues
- white and gray matter

Anisotropy of white matter
- preferential fluid flow and diffusion along white matter tracts (rostral-caudal dir.)

No lymphatics

Extracellular diffusive and convective transport

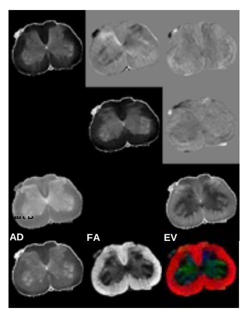
Binding, degradation, endocytosis, and intracellular kinetics



NMR of the rat spinal cord (T12)

Diffusion Tensor Imaging

Restricted motion of water molecules in tissue

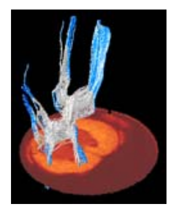


Pulsed-gradient spin echo sequence

Stejskal-Tanner equation: $S_i = S_0 \exp(-b_{ij} D_{ij})$

$\mathbf{D}_e$ estimated via multivariate regression models

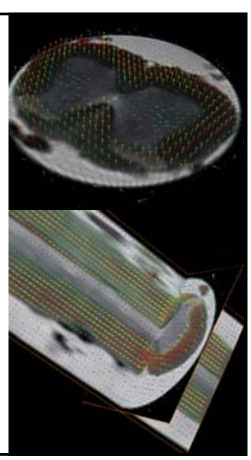
Resolution: 60 x 60 x 300 μm^3



Rat cord: DTI maps & Fibers in the spinal cord (T. Mareci)

Transport Anisotropy

- Calculated pixel by pixel from the DTI derived $\mathbf{D}_e$.
- Effective diffusion tensor eigenvectors $\mathbf{V} = [\mathbf{v}_1\ \mathbf{v}_2\ \mathbf{v}_3]$.
- $\boldsymbol{k} = \mathbf{V} \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix} \mathbf{V}^T$
- Eigenvalues, λ_i, were estimated previously for albumin
- Map direction of maximum transport (<u>eigenvector of maximum eigenvalue</u>)



What is a Porous Medium?

Porous Media:
- Solid matrix filled throughout by a network of interconnected pores
- Saturated with a incompressible fluid
- Velocity is proportional to the pressure gradient

$\mathbf{u} = -\mathbf{k} \cdot \nabla p$ (Darcy's Law)

hydraulic conductivity tensor

Poroelastic Media:
- Matrix exhibits elastic deformation behavior

Governing Equations

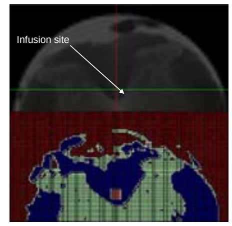
Porous medium
- Rigid solid matrix
- Saturated with viscous incompressible fluid

Conservation equations
- Fluid mass: $\nabla \cdot \mathbf{u} = 0$
- Momentum (Darcy's law): $\mathbf{u} = -\mathbf{k} \cdot \nabla p$

  where $\mathbf{u}$ is volume averaged velocity
- Albumin (benchmark study): $\phi \dfrac{\partial C}{\partial t} + \nabla \cdot (\mathbf{u}C) = \nabla \cdot (\phi \mathbf{D} \nabla C)$
  - MW = 66,000
  - No protein degradation
  - No binding

Tissue Segmentation

Spinal Cord Region	S_o range ($1 \le z \le 59$)	S_o range ($60 \le z \le 80$)
White matter	$0 \le S_o < 0.412$	$0 \le S_o < 0.455$
Gray matter	$0.412 \le S_o < 0.558$	$0.455 \le S_o < 0.600$
Background	$0.558 \le S_o \le 1$	$0.600 \le S_o \le 1$



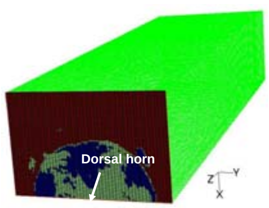
FE Computational Model

Fluent
- Segregated solver
- Implicit formulation
- Node based gradients

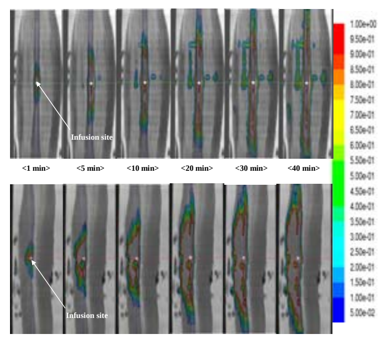
Porous media formulation
- Modify Cons. of Momentum

Weakly coupled solution

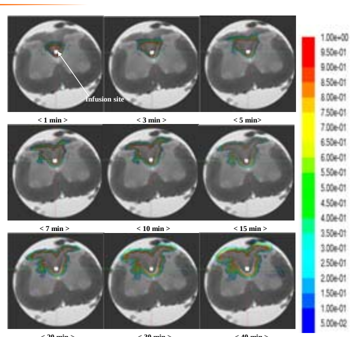
Tracer Transport Equation
- user-defined anisotropic diffusion source term
- Fixed time steps



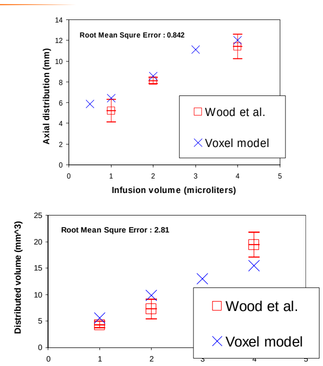
Axial Albumin Tracer Distribution



Transverse Albumin Tracer Distribution

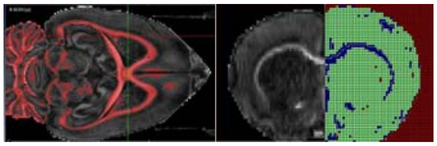


Validation Distribution Studies in the Spinal Cord



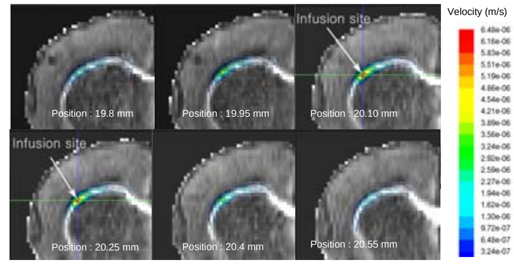
Modeling CED into the Corpus Callosum

Segmentation using FA values

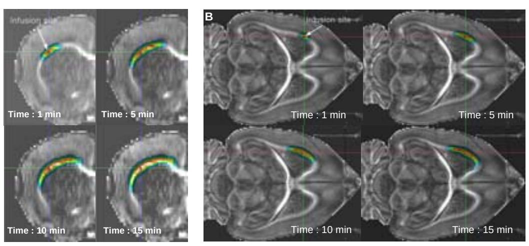


Tissue region	FA Range
White matter	0.33~1
Gray matter	0.11~0.33
CSF & background	0~0.11

CED into the Corpus Callosum: Velocity Contours



Albumin Infusion into the Corpus Callosum



Conclusions & Future Work

- Developed a methodology to estimate interstitial pressure, velocity fields, and interstitial transport
- The semi-automatic approach allows for rapid estimation of macromolecular tracer distributions following CED
- Provide a process for incorporating realistic and more complex anatomical boundaries.
- Validated methodology by comparing with experimental distribution data for the spinal cord
- Additional studies comparing these predicted distributions with measured tracer transport in the brain are required.

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Dr. Paul Carney

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NIH Grant R21 NS052670

Imaging Animal Models of Brain Disease

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Division of Experimental Neurology and Neurological Surgery

Washington University School of Medicine

St. Louis, MO 63110

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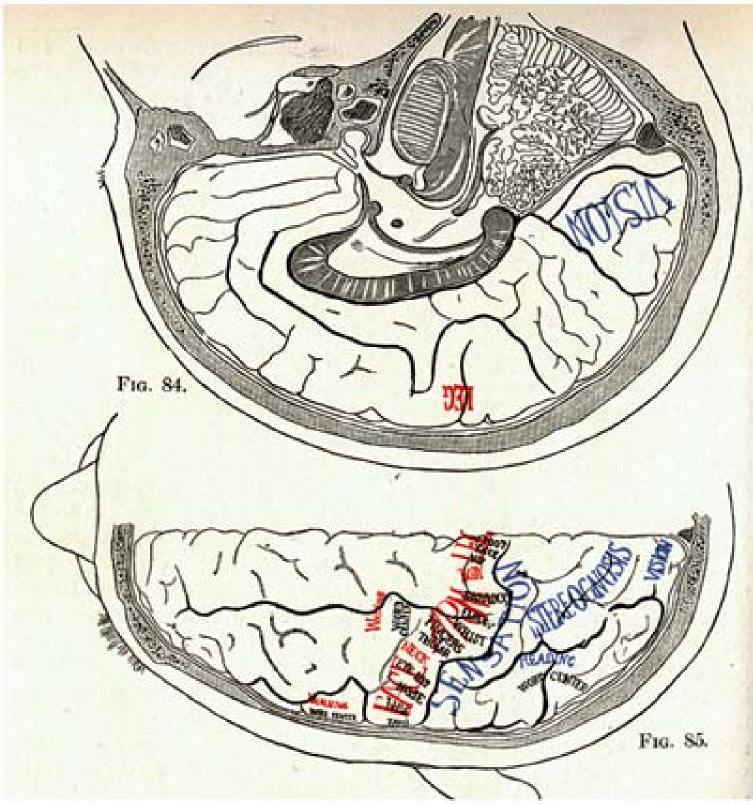
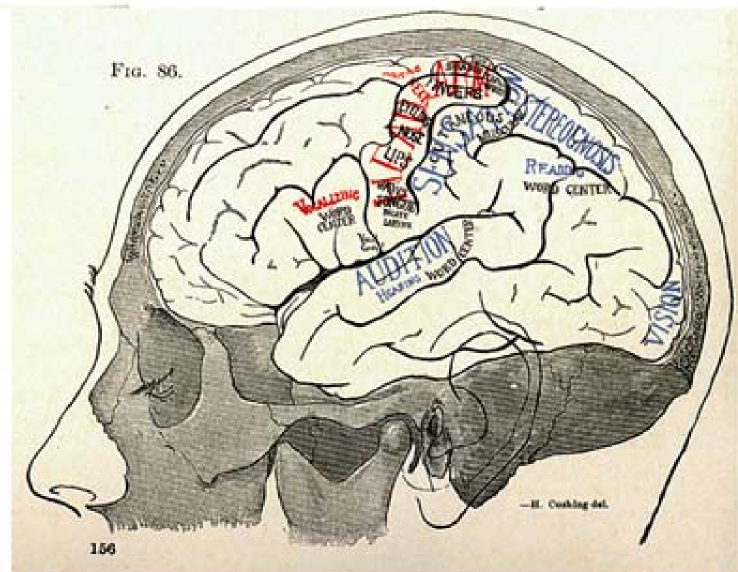
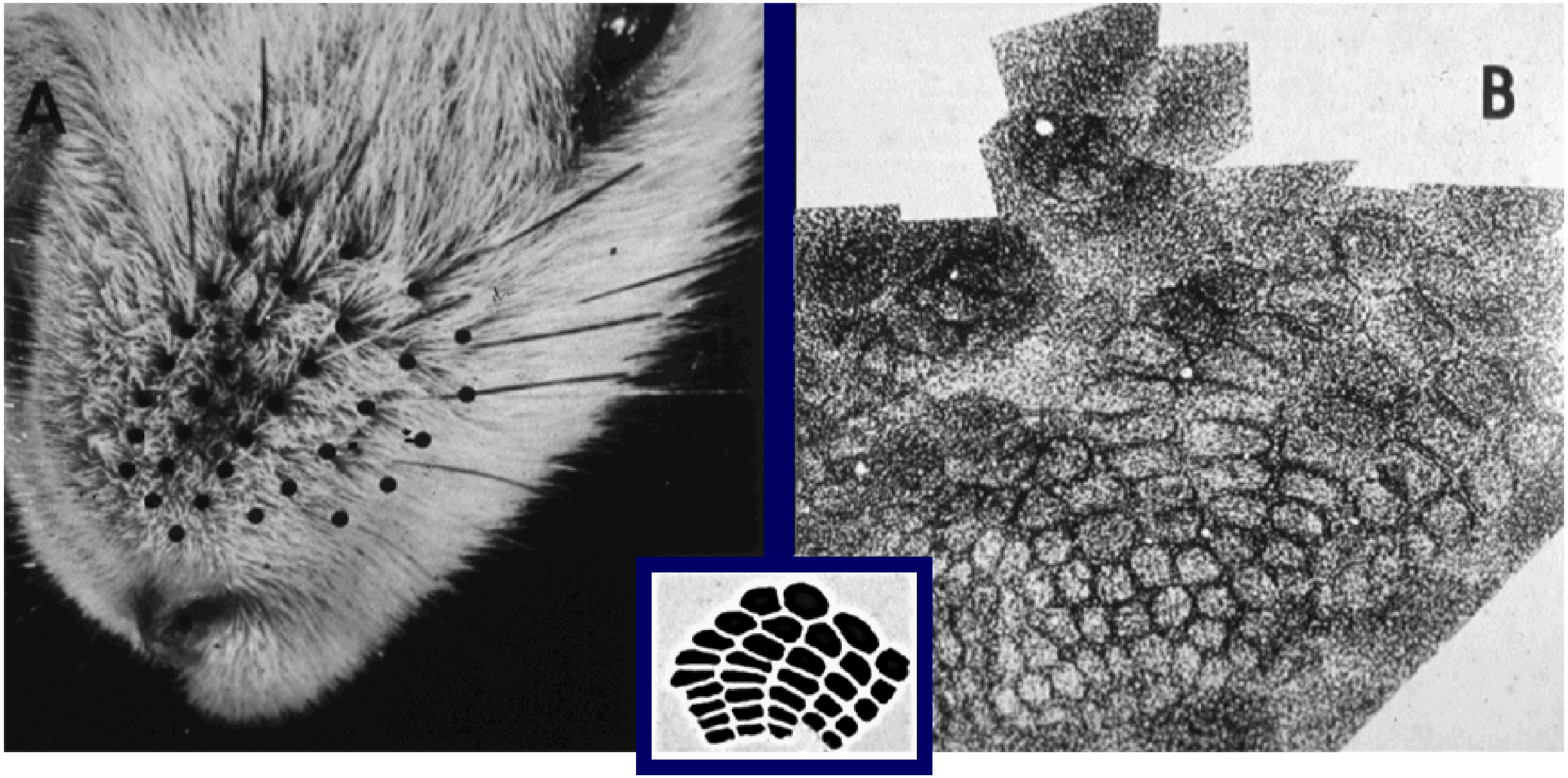
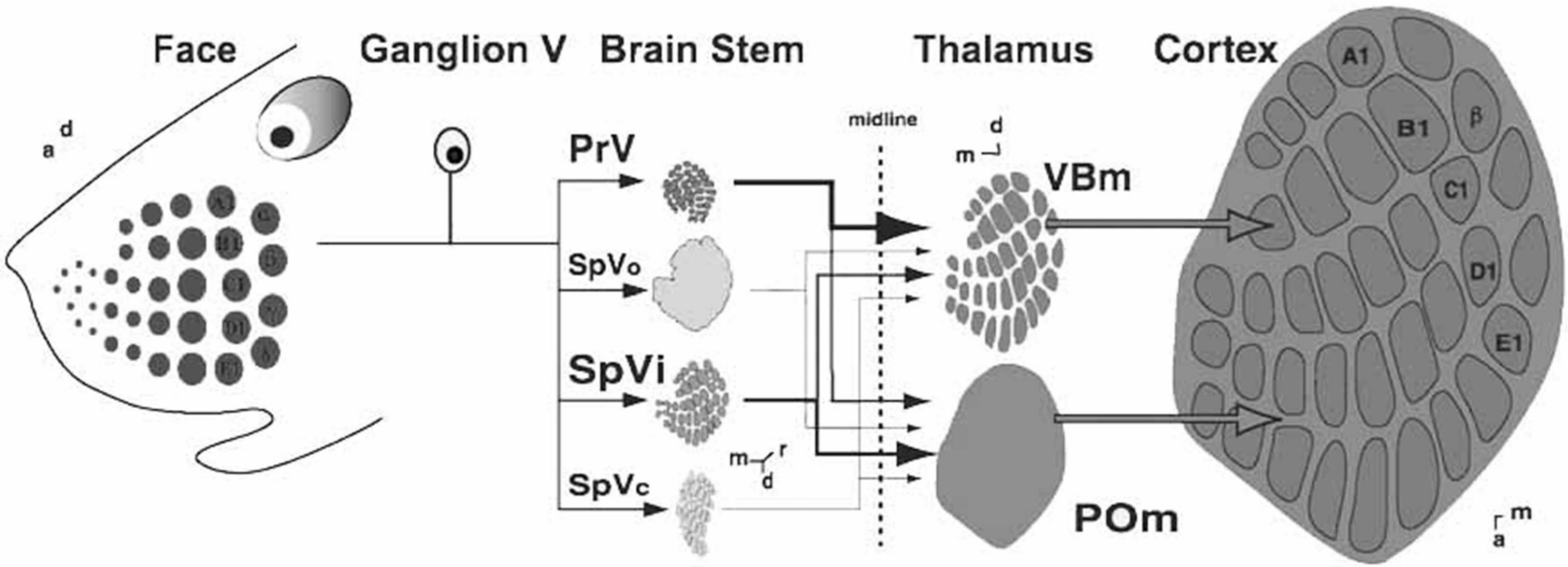
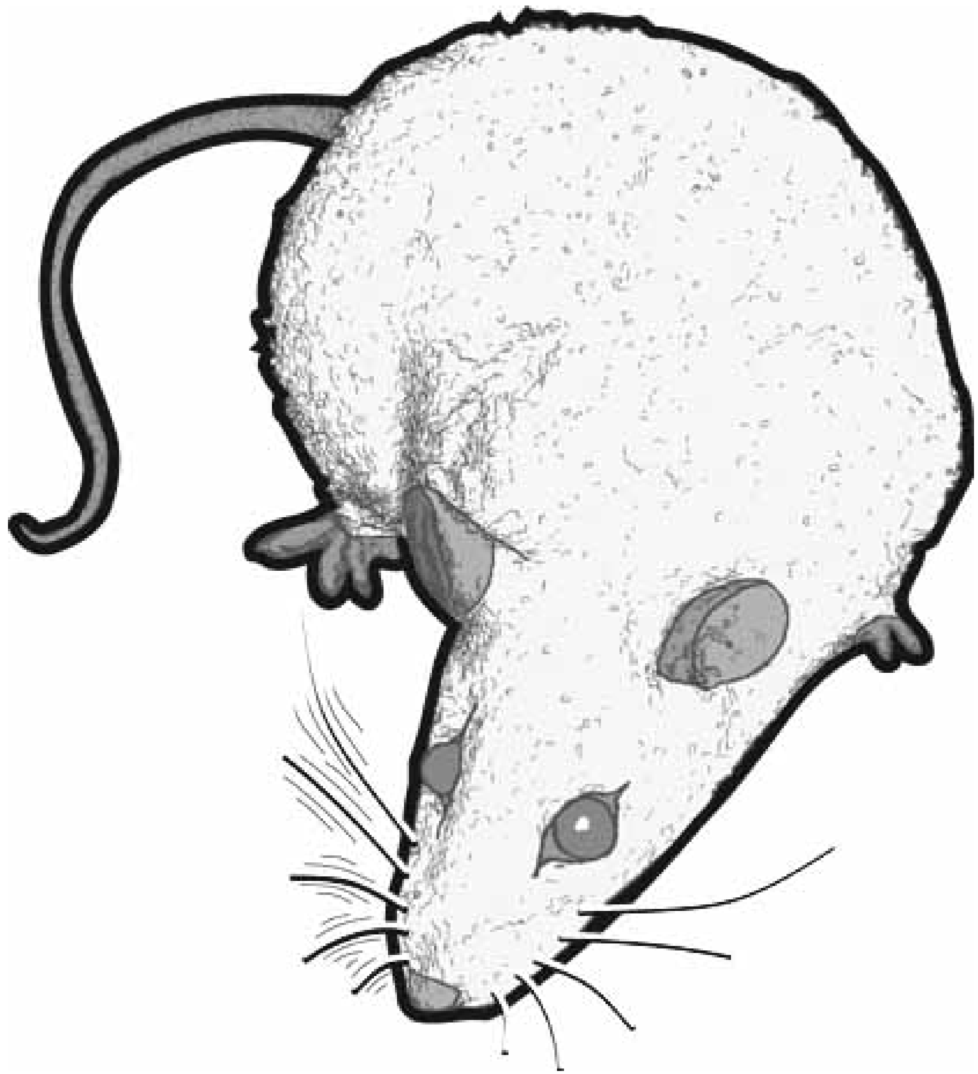




From Keen’s Surgery, 1919


A
B


Face
Ganglion V
Brain Stem
Thalamus
Cortex
a
d
PrV
SpVo
SpVi
SpVc
midline
m
d
VBm
POm
m
r
d
A1
B1
β
C1
D1
E1
m
a



References - A Model System

Woolsey TA, Van der Loos H 1970 The structural organization of layer IV in the somatosensory region (SI) of mouse cerebral cortex: the description of a cortical field composed of discrete cytoarchitectonic units. Brain Res *17*:205-242.

Woolsey, TA 2003 Barrel cortex. [cited September 27, 2005. Available from http://www.ibro.info/Pub_Main_Display.asp?Main_ID=21.]

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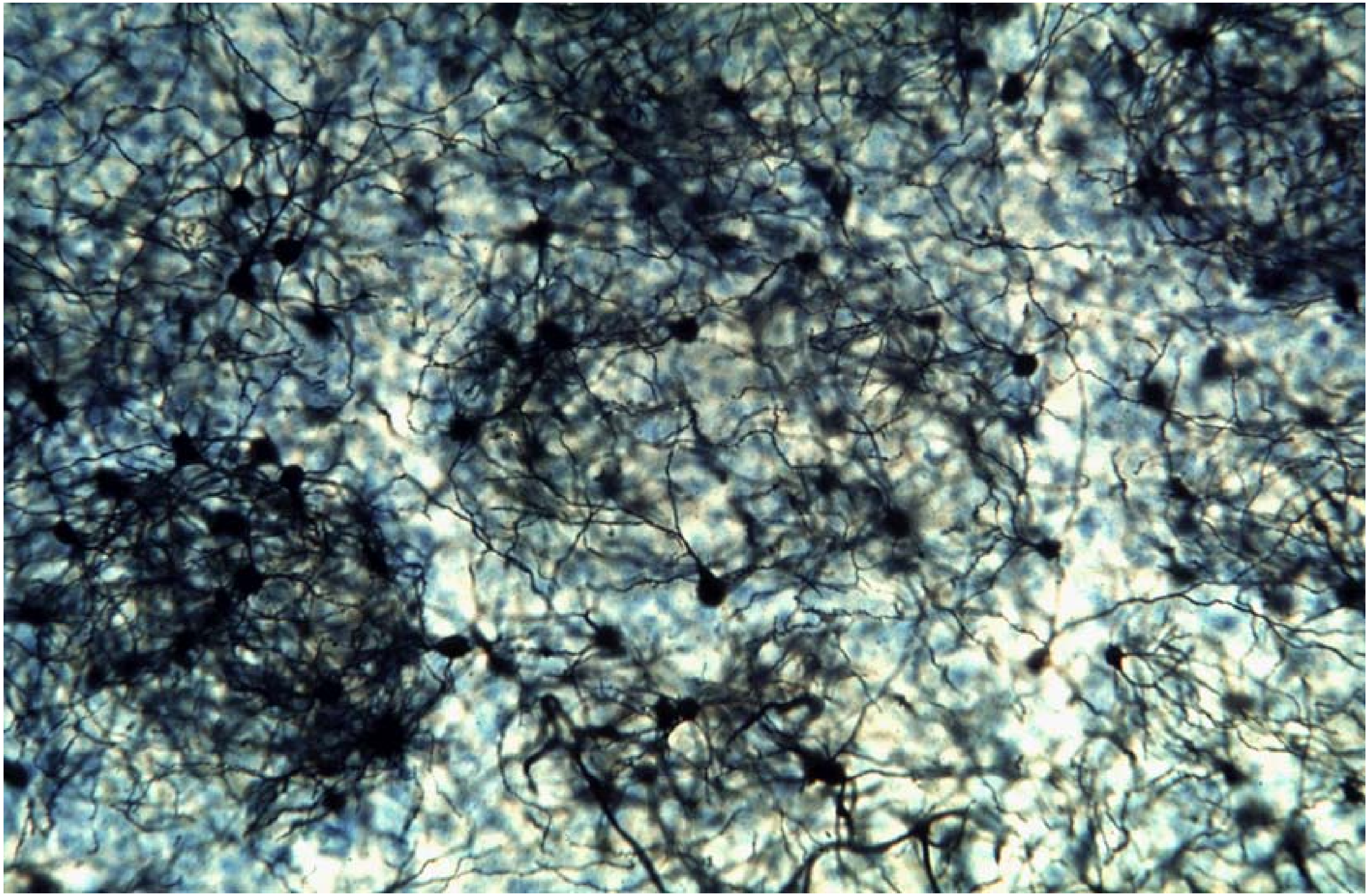
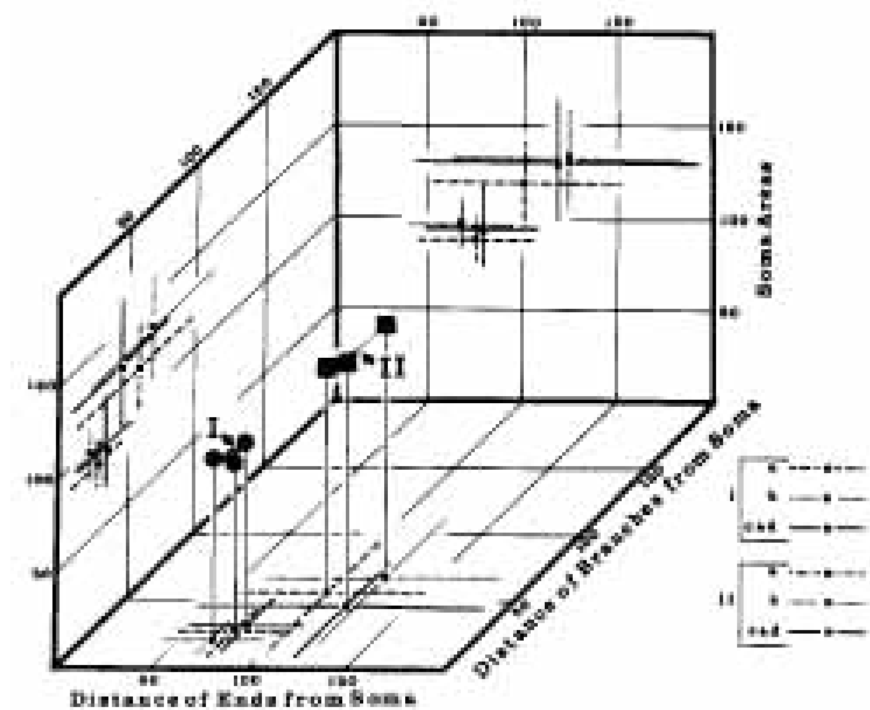
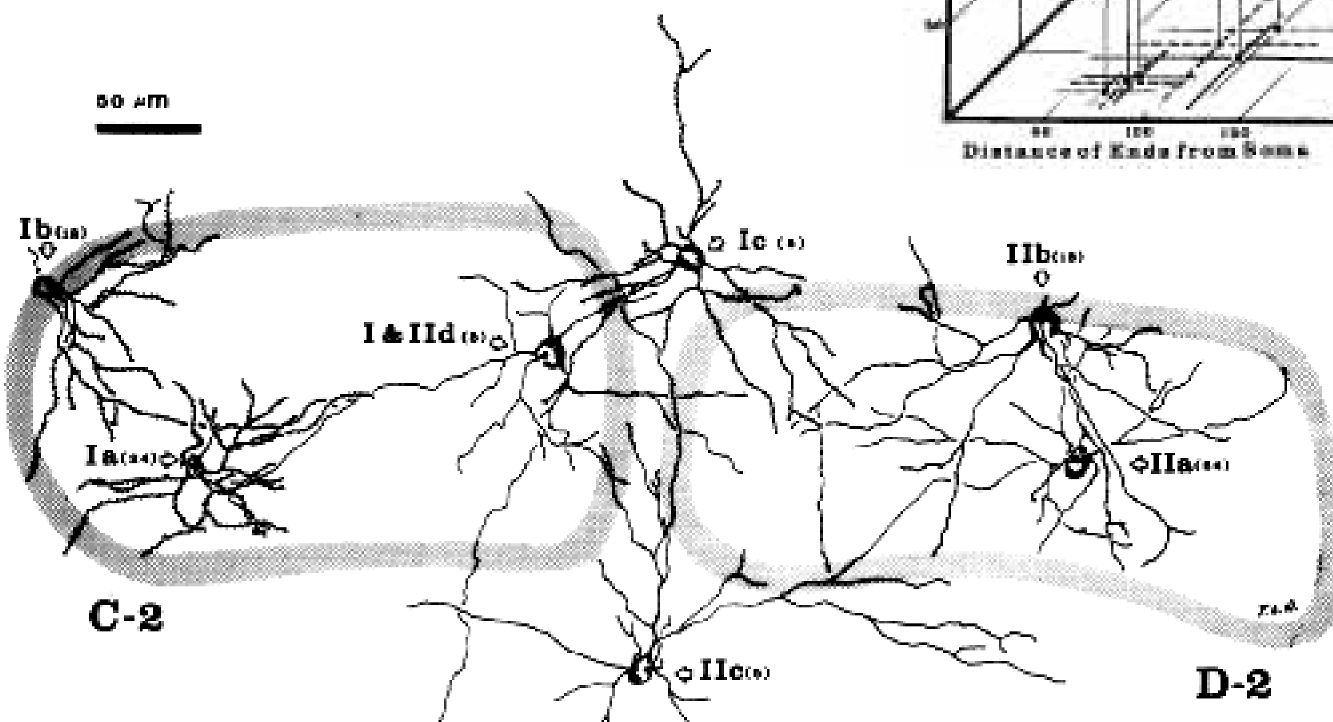
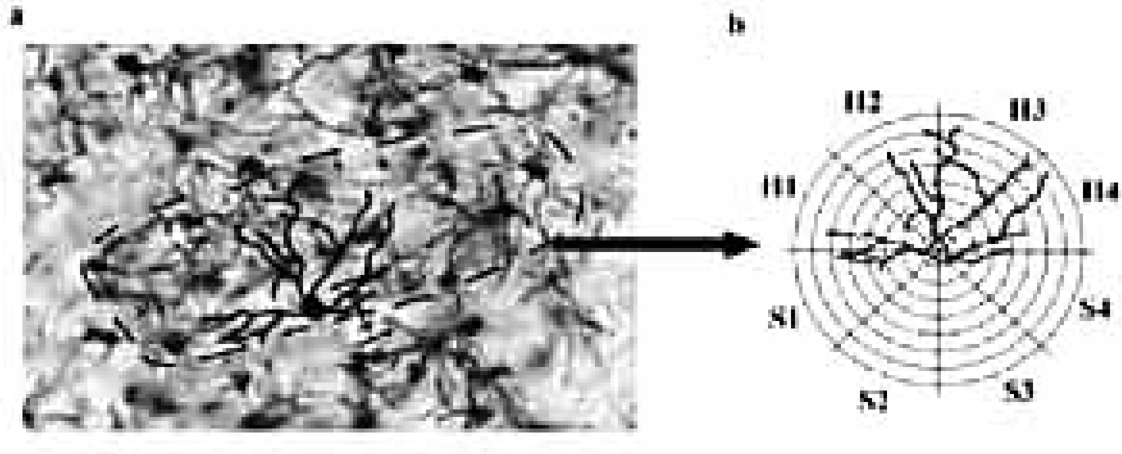
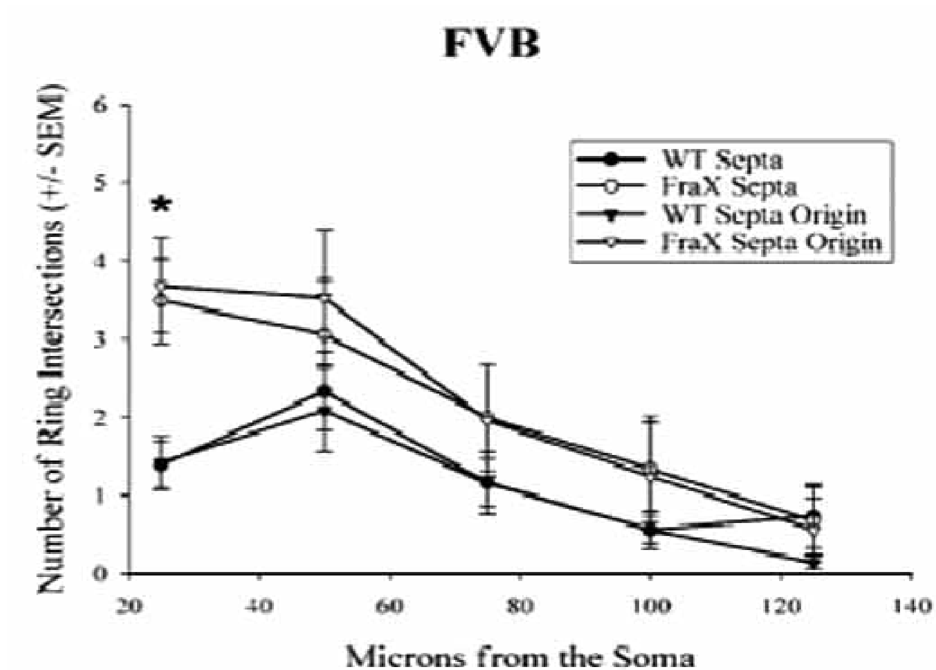



Soma Areas
Distance of Branches from Soma
Distance of Ends from Soma
I
II


50 µm
Ib
Ic
I & IId
IIb
Ia
IIa
IIc
C-2
D-2


a
b
H2
H3
H1
H4
S1
S4
S2
S3


FVB
Number of Ring Intersections (+/- SEM)
Microns from the Soma
WT Septa
FraX Septa
WT Septa Origin
FraX Septa Origin
*
0
1
2
3
4
5
6
20
40
60
80
100
120
140

References - Axons, Dendrites, Fragile X

Wann DF, Woolsey TA, Dierker ML, Cowan WM 1973 An on-line digital computer system for the semi-automatic analysis of Golgi-impregnated neurons. IEEE Trans BME *20*:223-247.

Woolsey TA, Dierker ML,Wann DF 1975 Mouse SmI cortex: qualitative and quantitative classification of Golgi-impregnated barrel neurons. Proc Natl Acad Sci USA *72*:2165-2169.

Harris RM, Woolsey TA 1983 Computer-assisted analyses of barrel neuron axons and their putative synaptic contacts. J Comp Neurol *220*:63-79.

Galvez R, Gopal AR, Greenough WT 2003 Somatosensory cortical barrel dendritic abnormalities in a mouse model of the fragile X mental retardation syndrome. Brain Res *971:*83-89.

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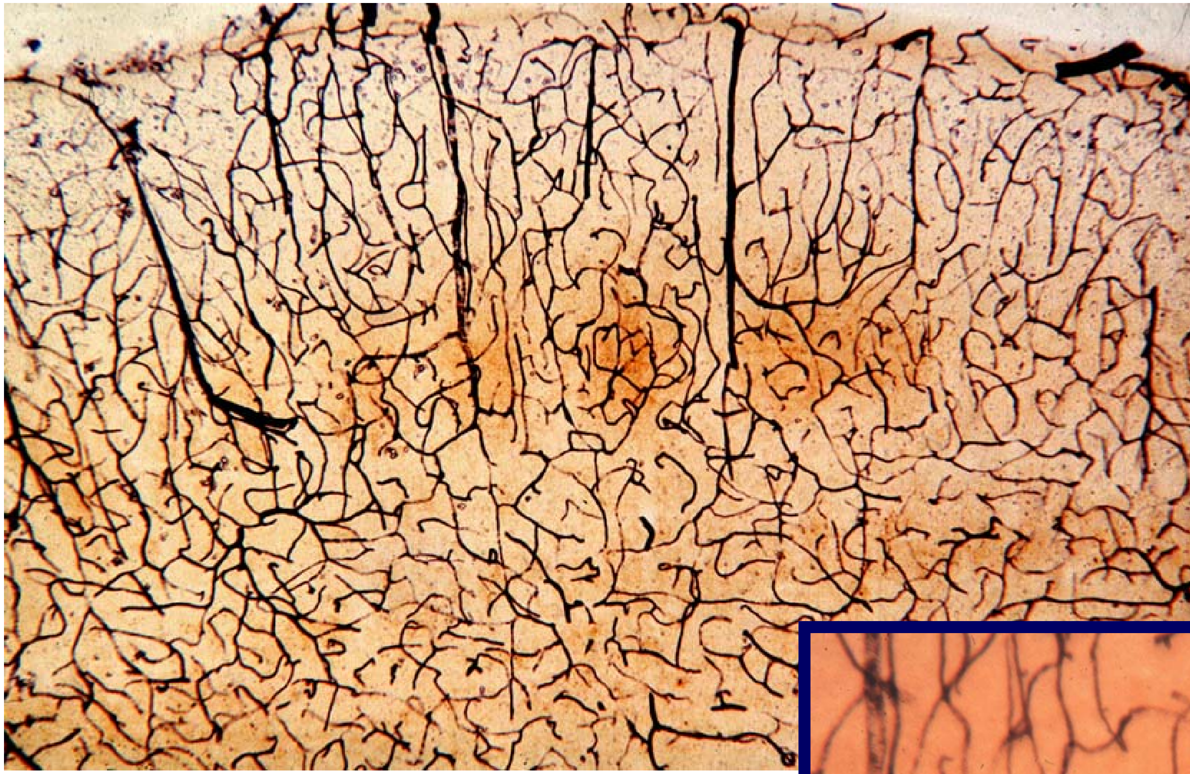
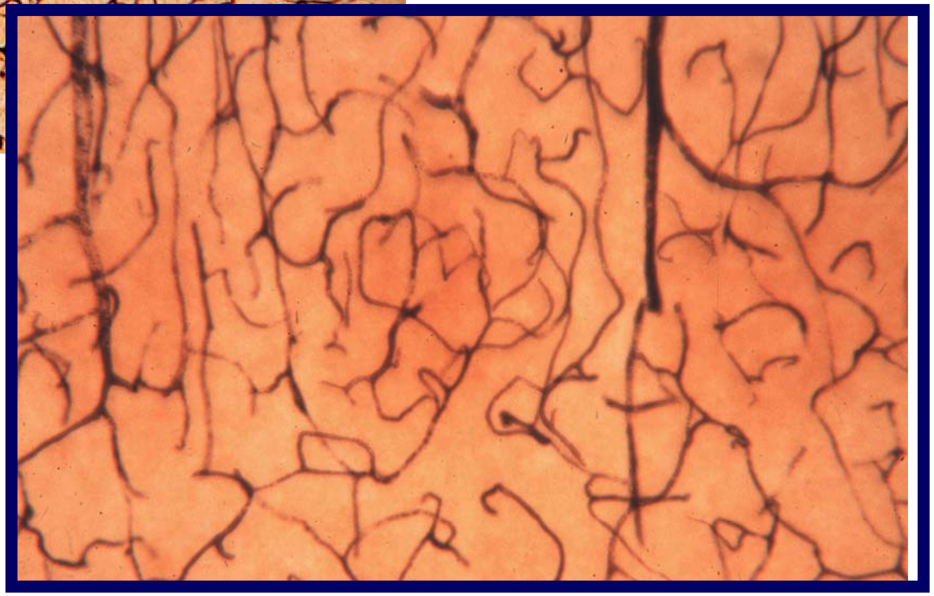
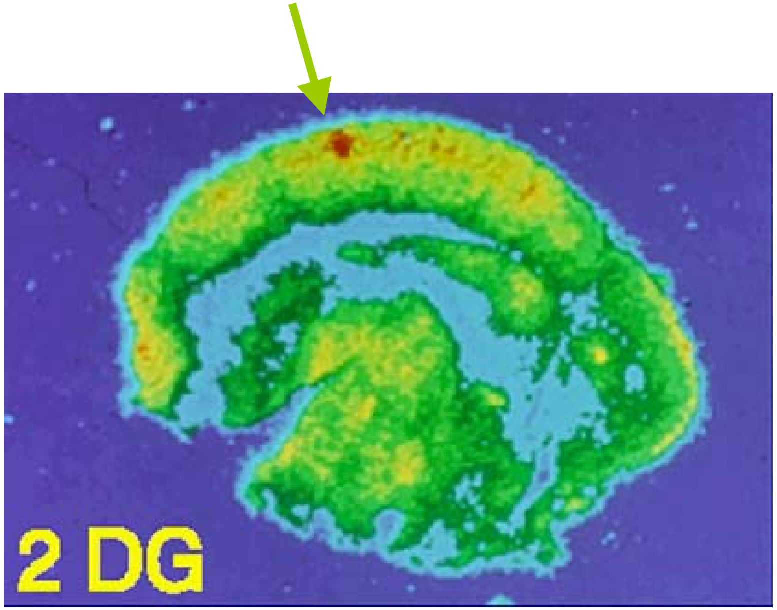
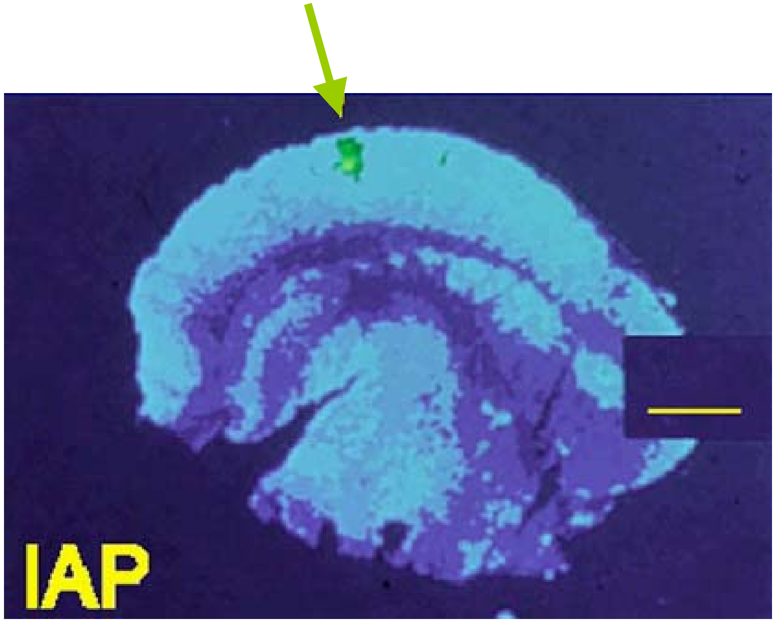
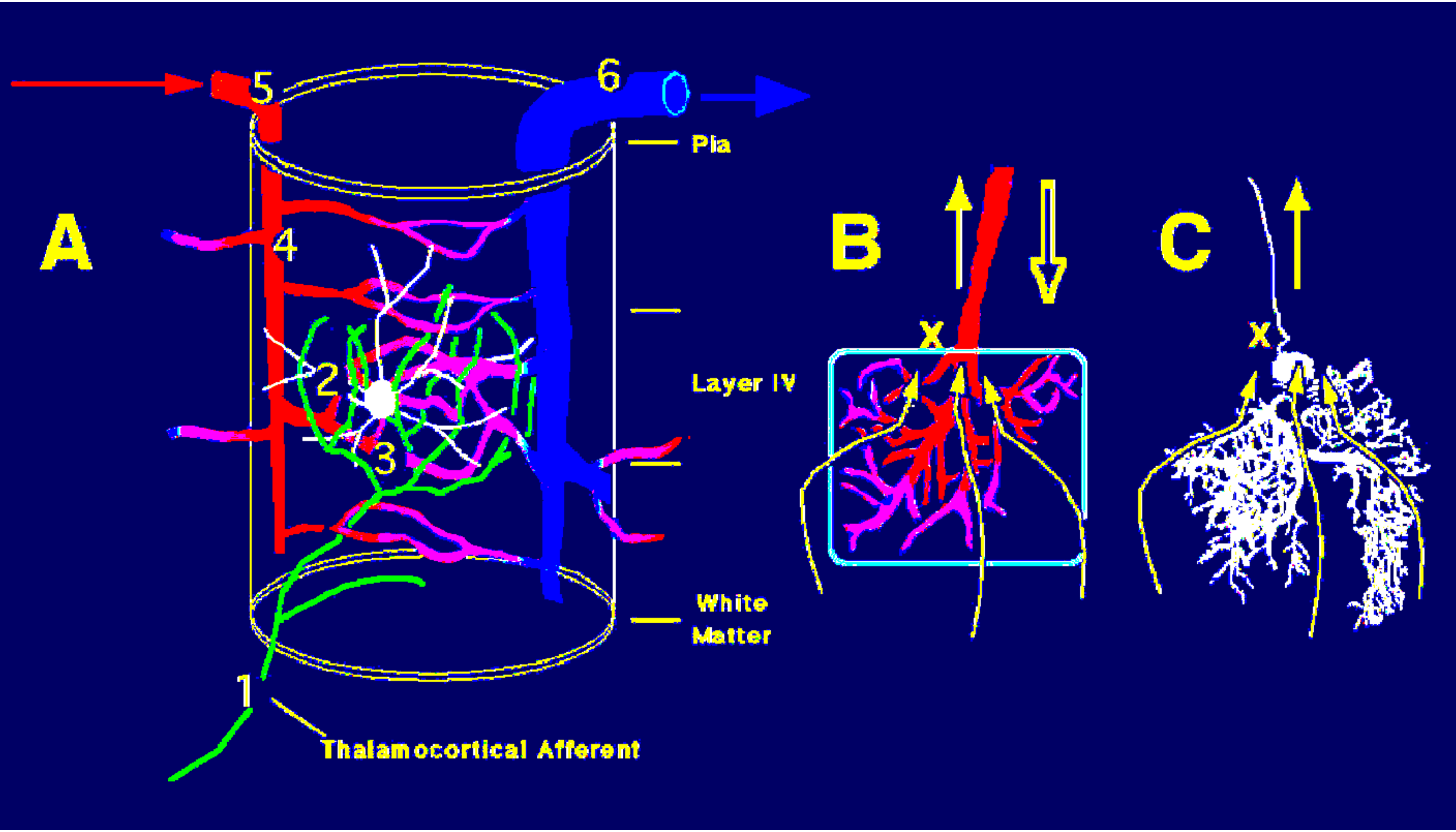


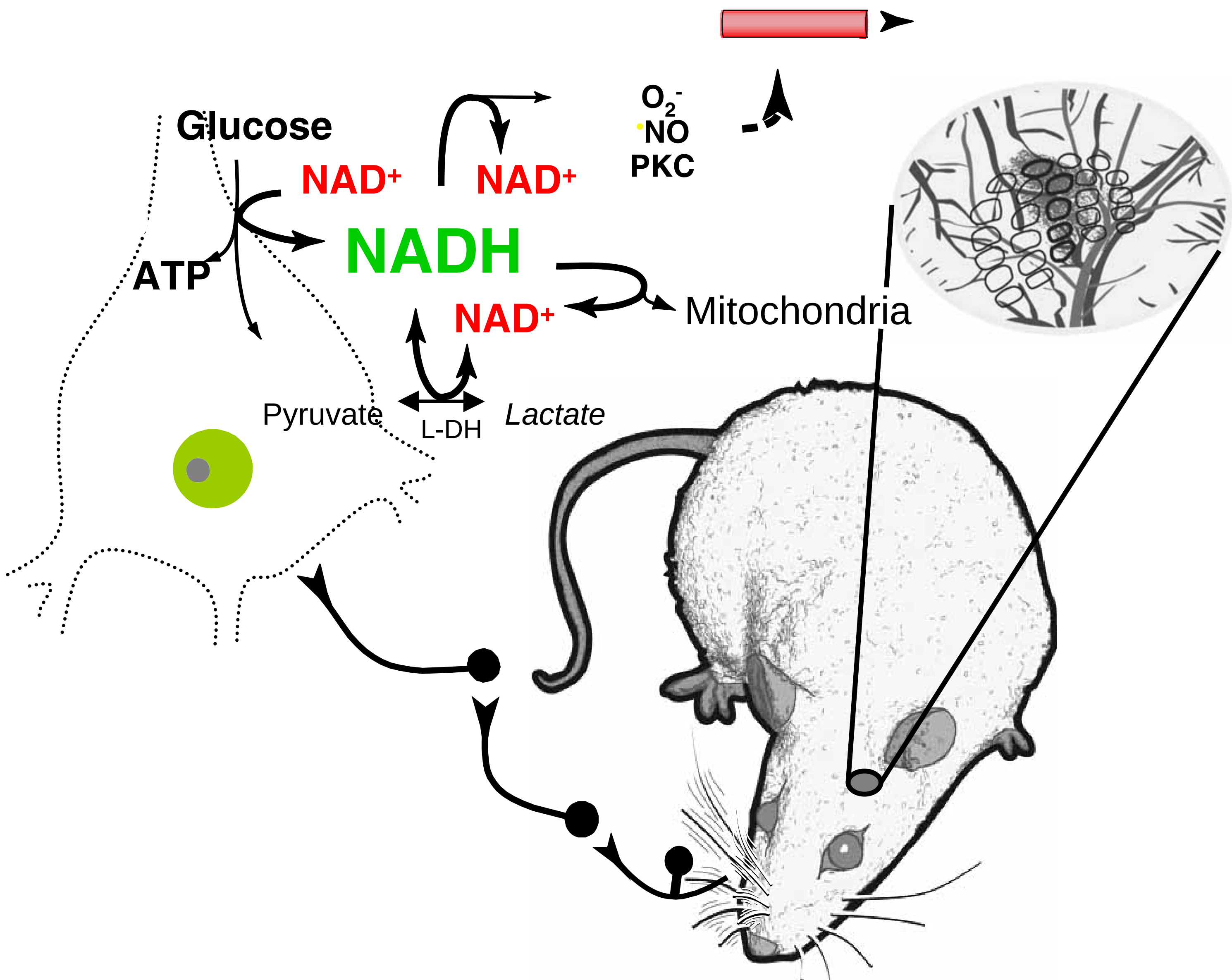



2 DG


IAP



A
5
6
Pia
4
2
Layer IV
3
White
Matter
1
Thalamocortical Afferent
B
X
C
X



Glucose
NAD+
NAD+
O_2^-
•NO
PKC
ATP
NADH
NAD+
Mitochondria
Pyruvate
L-DH
Lactate

References - Blood Flow

Woolsey TA, Rovainen CM, Cox SB, Henegar MH, Liang GE, Liu D, Moskalenko YuE, Sui J, Wei L 1996 Neuronal units linked to microvascular modules in cerebral cortex: response elements for imaging the brain. Cerebral Cortex *6*:647-660.

Boero J, Ascher J, Arregui A, Rovainen C, Woolsey TA 1999 Increased brain capillaries in chronic hypoxia. J Appl Physiol *86*:1211-1219.

Ido Y, Chang K, Woolsey TA, Williamson JR 2001 NADH: sensor of blood flow need in brain and muscle. FASEB J *15:*1419-21.

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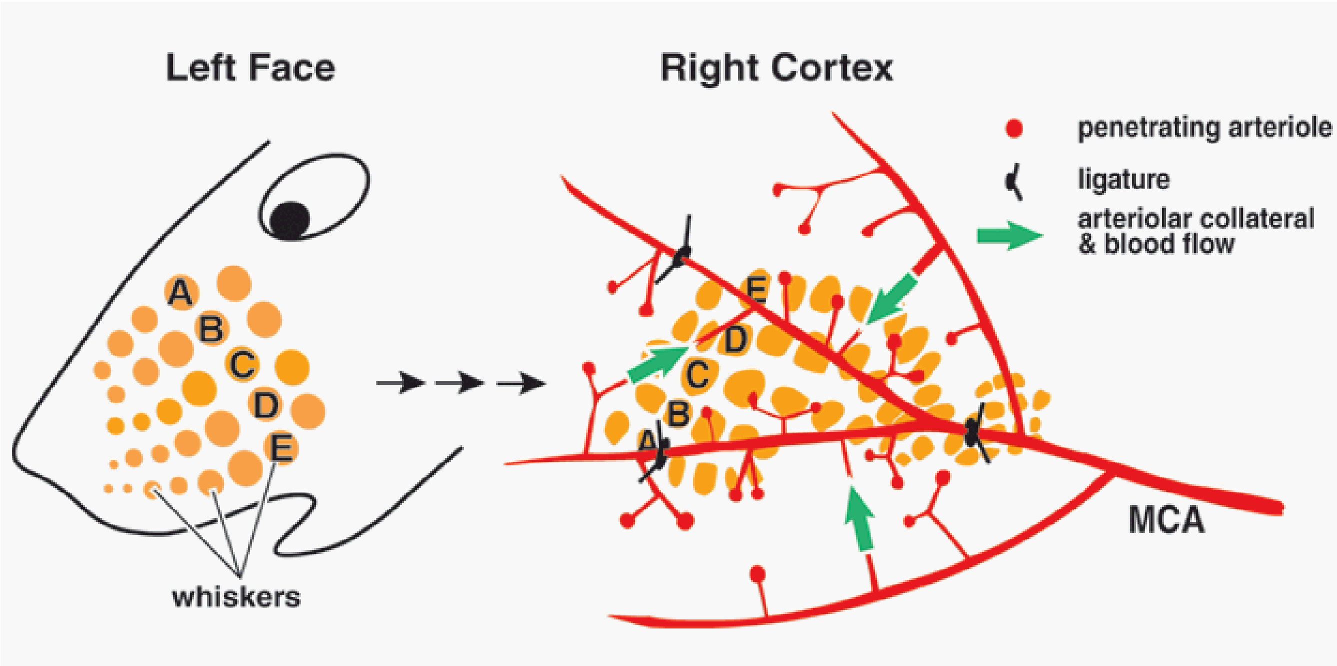
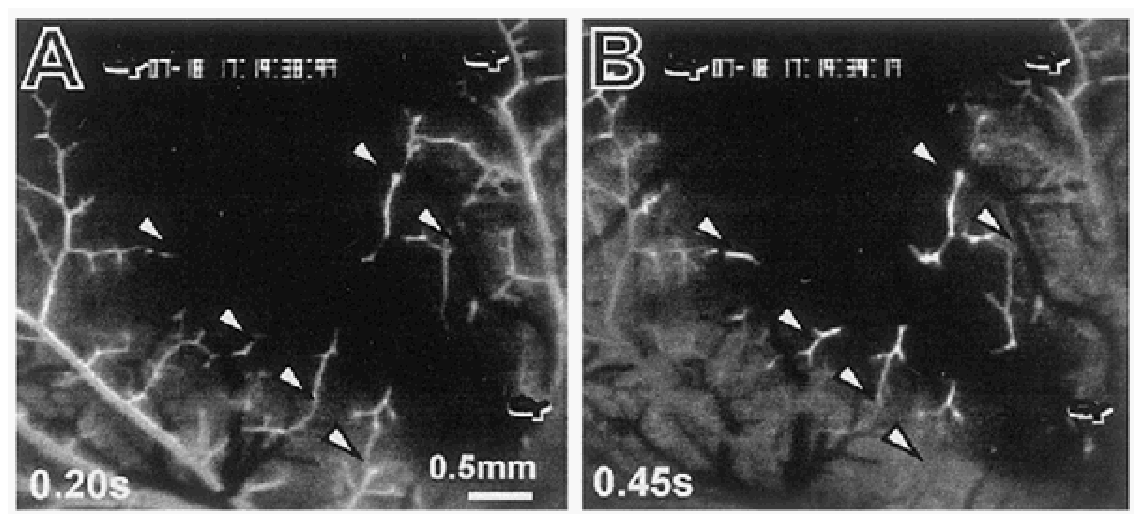
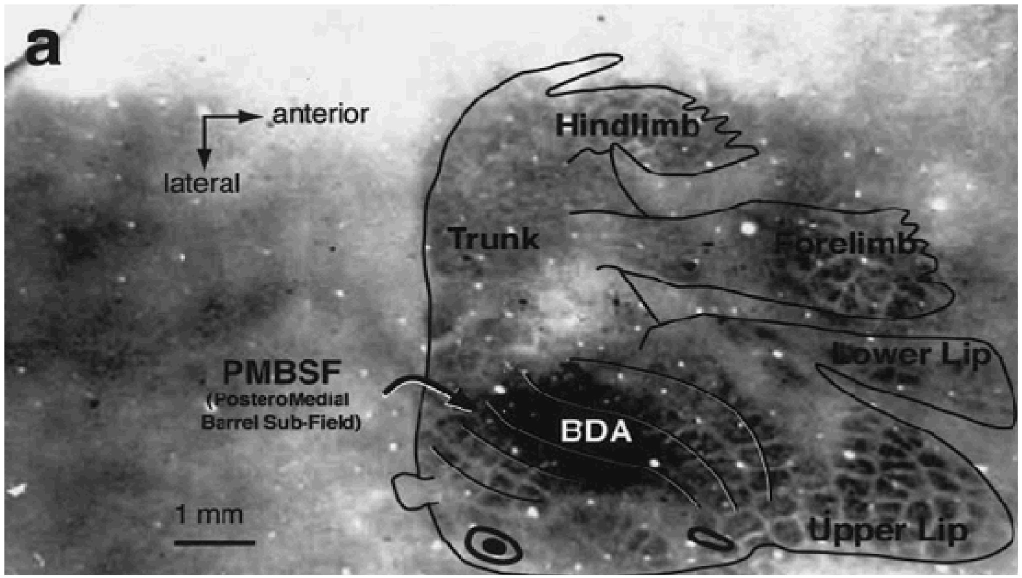
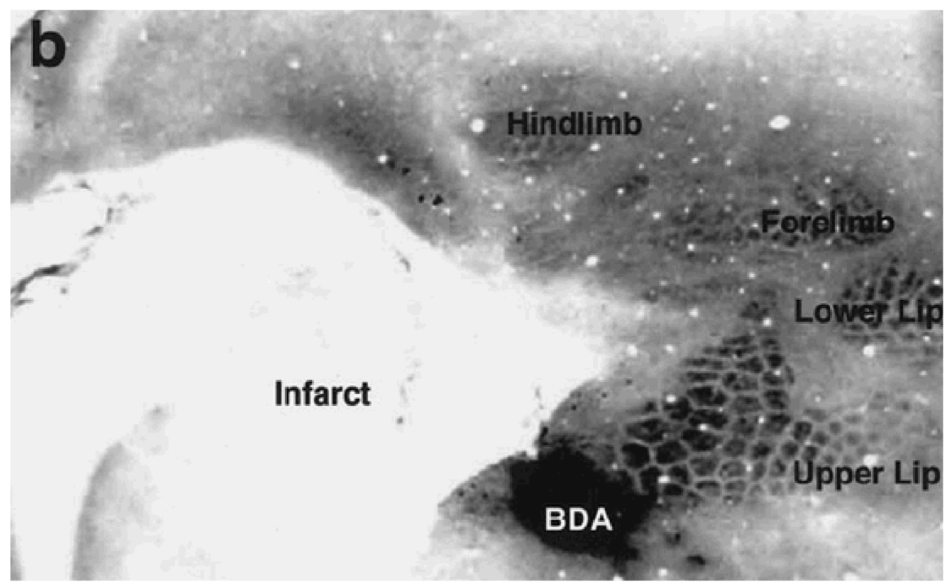
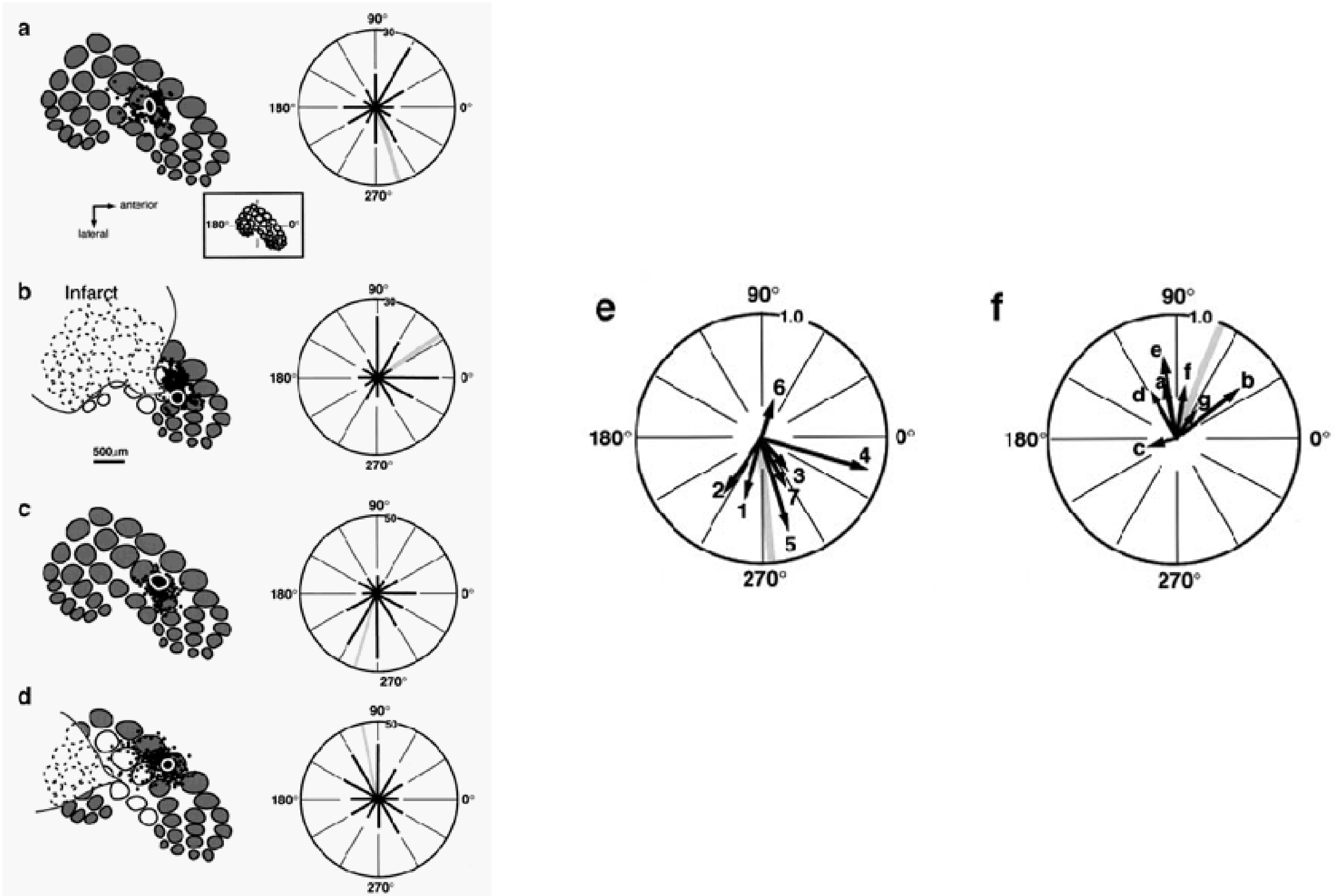

Left Face
Right Cortex
penetrating arteriole
ligature
arteriolar collateral
& blood flow
A
B
C
D
E
whiskers
MCA

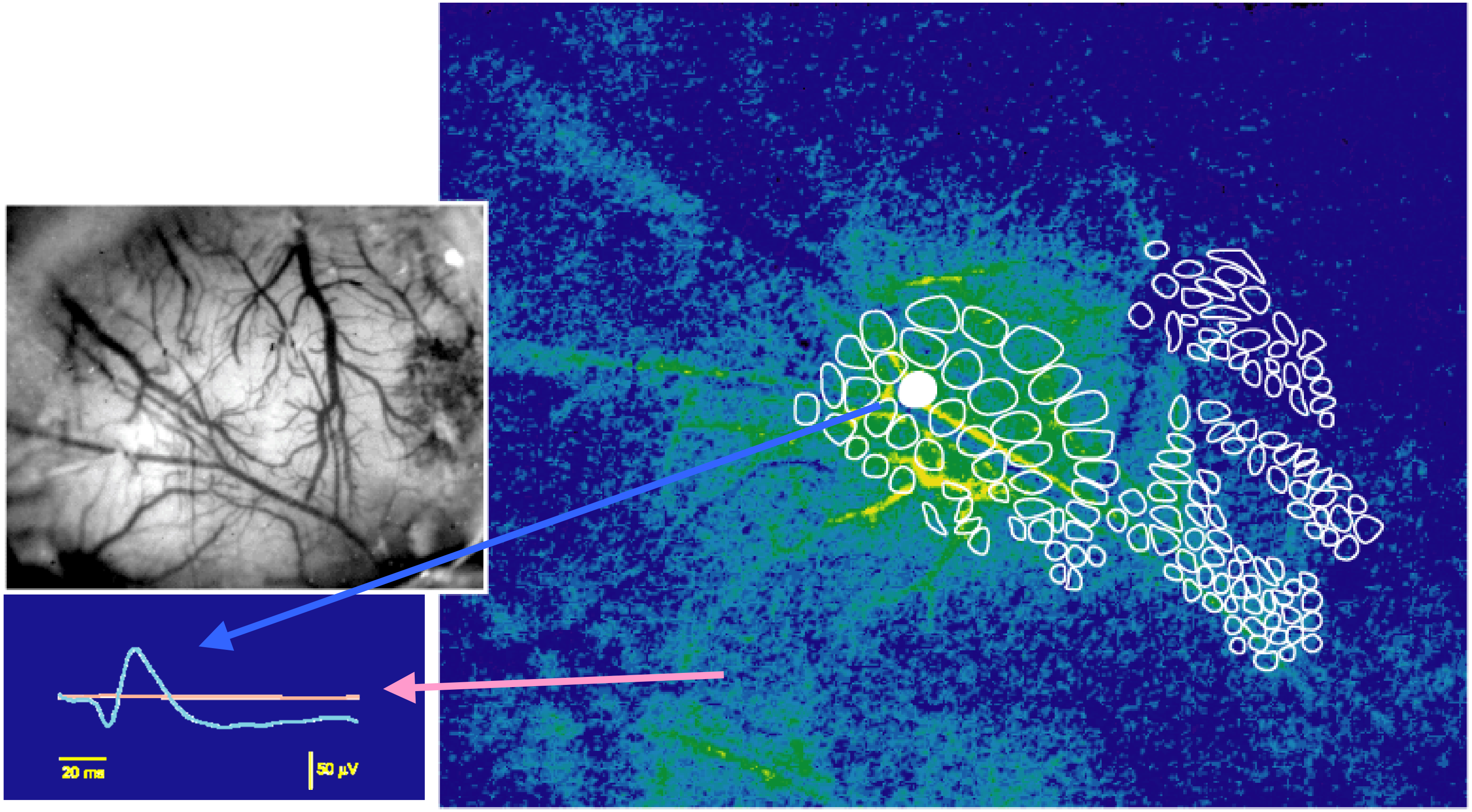

A
B
0.20s
0.5mm
0.45s


a
anterior
lateral
Hindlimb
Trunk
Forelimb
Lower Lip
PMBSF
(PosteroMedial
Barrel Sub-Field)
BDA
1 mm
Upper Lip

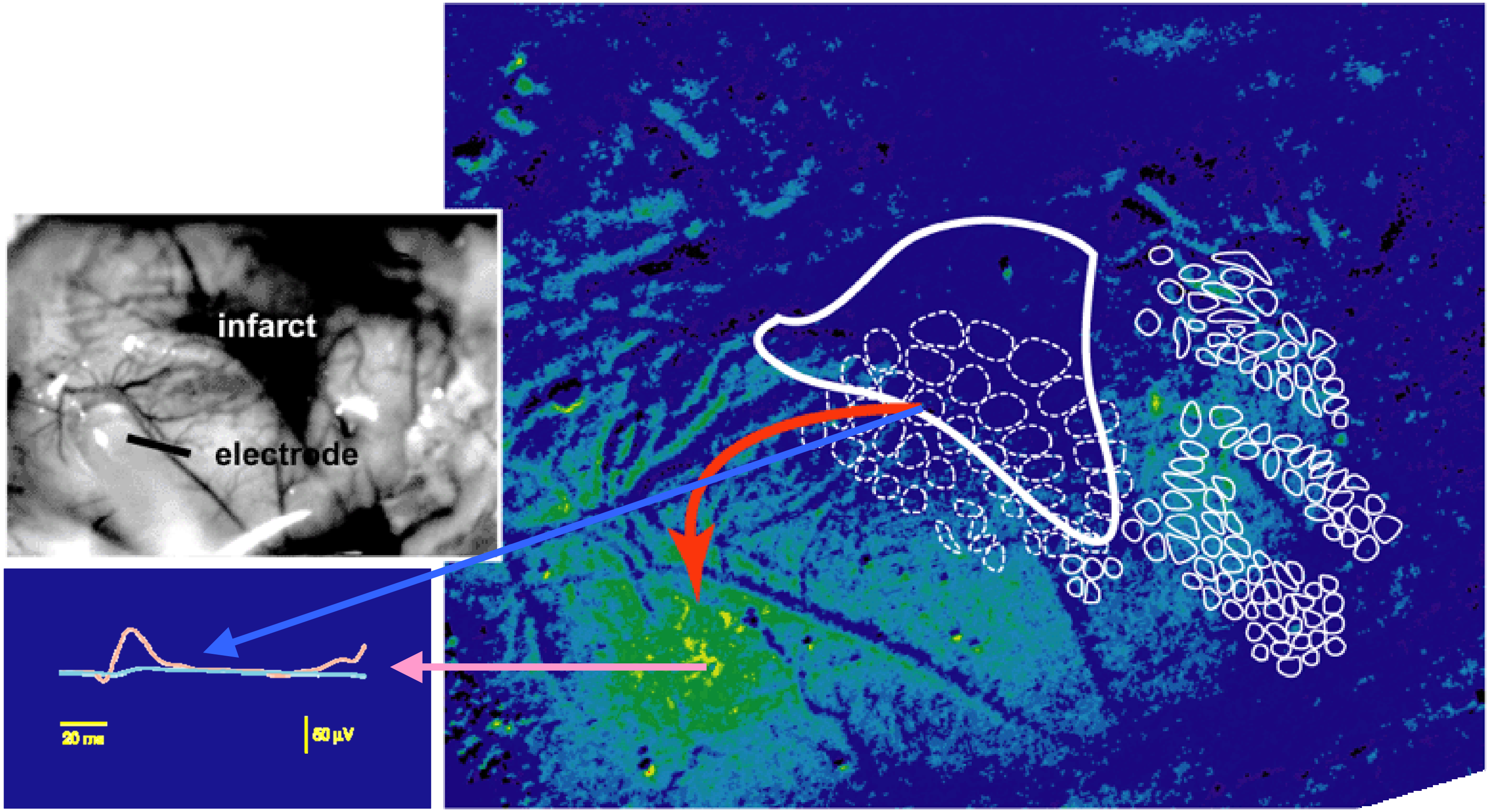

b
Hindlimb
Forelimb
Lower Lip
Infarct
Upper Lip
BDA


a
90°
30
180°
0°
270°
anterior
lateral
b
Infarct
500μm
c
50
d
e
1.0
6
4
3
7
2
1
5
f
e
a
f
d
g
b
c

Before “Ministroke”



30 days after “Ministroke”



References - Stroke

Wei L, Rovainen CM, Woolsey TA 1995 Ministrokes in rat barrel cortex. Stroke *26*:1459-1462.

Wei L, Craven K, Erinjeri J, Liang GE, Bereczki D, Rovainen CM, Fenstermacher JD, Woolsey TA 1998 Local cerebral blood flow during the first hour following acute ligation of multiple arterioles in rat whisker barrel cortex. Neurobiol Dis *5*:142-150.

Carmichael ST, Wei L, Rovainen CM, Woolsey TA 2001 New patterns of intra-cortical projections after focal cortical stroke. Neurobiol Dis *8*:910-922

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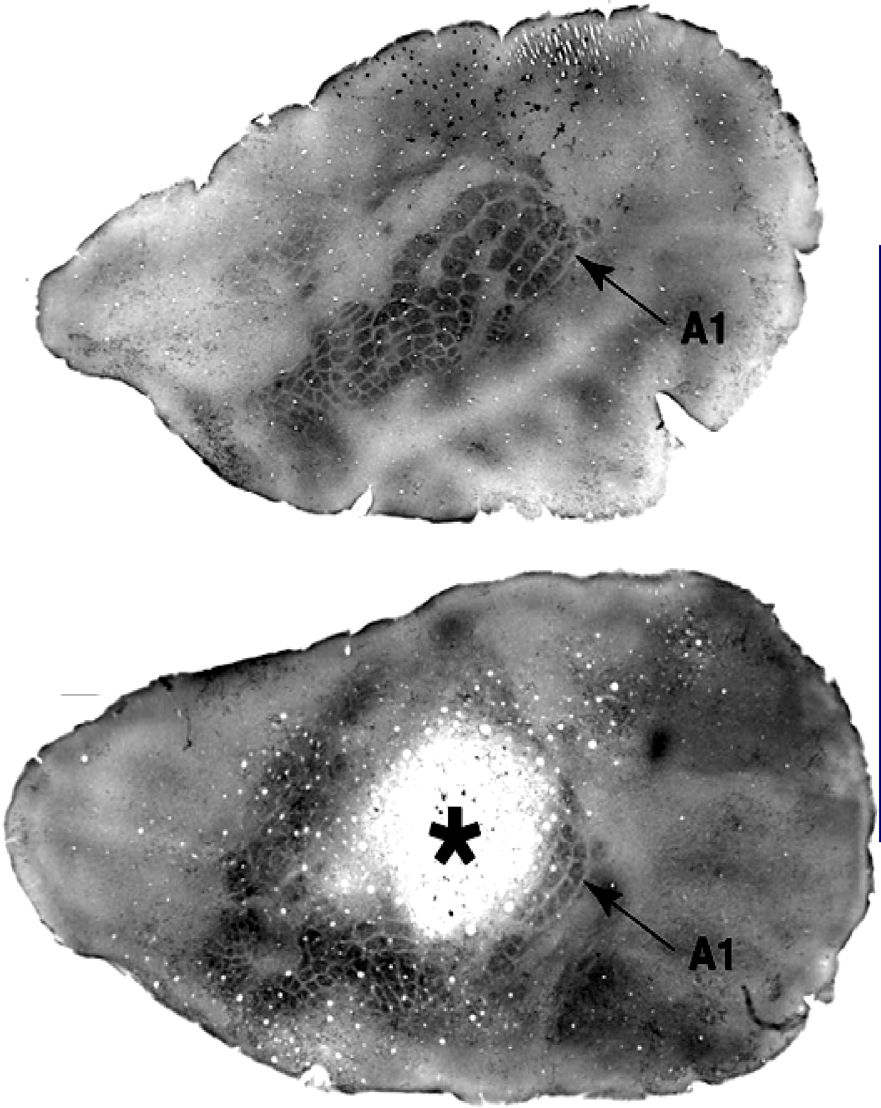
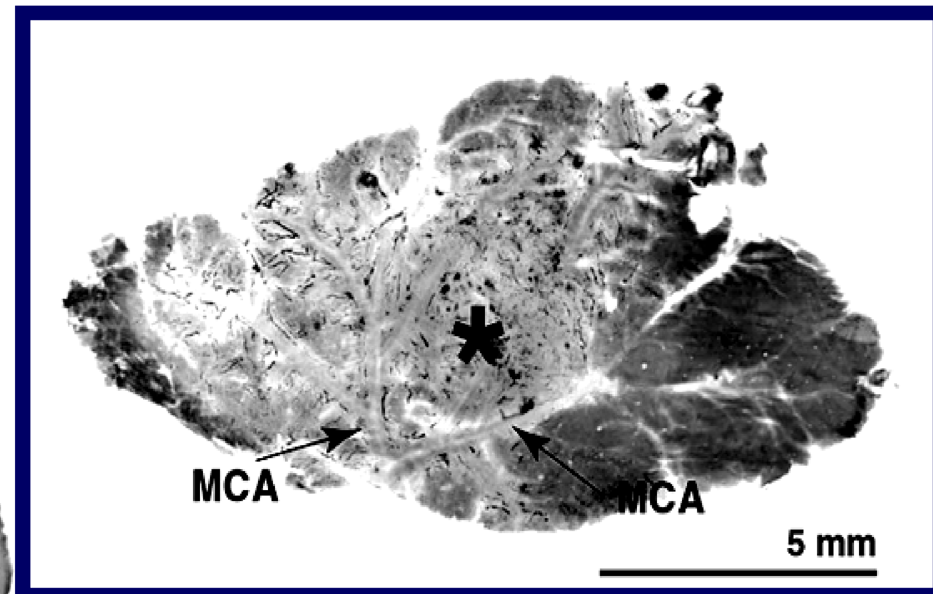
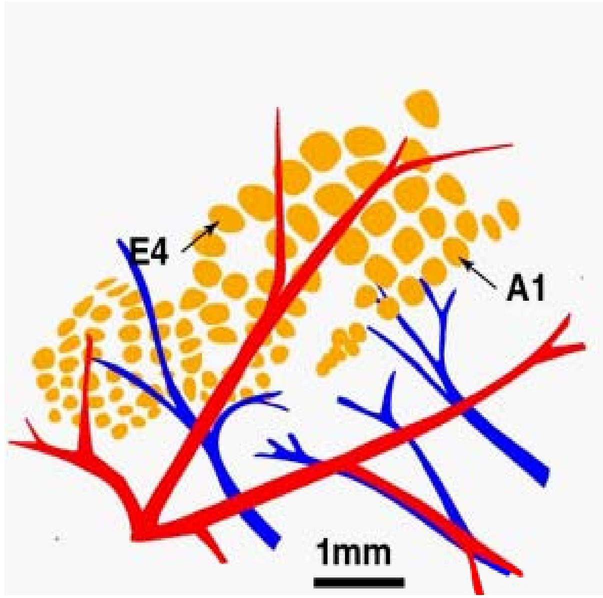
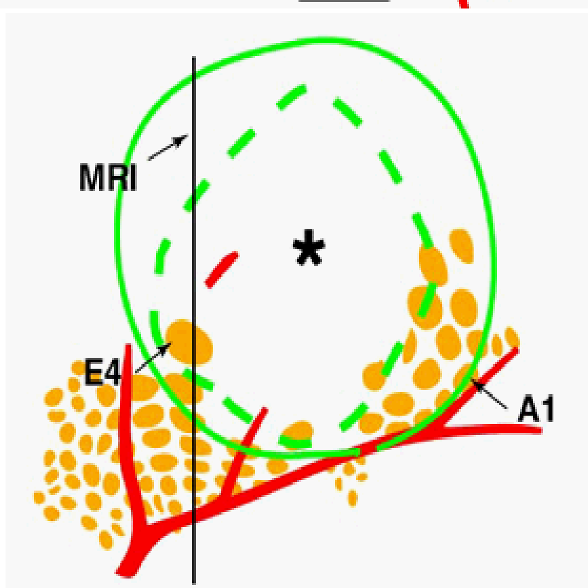
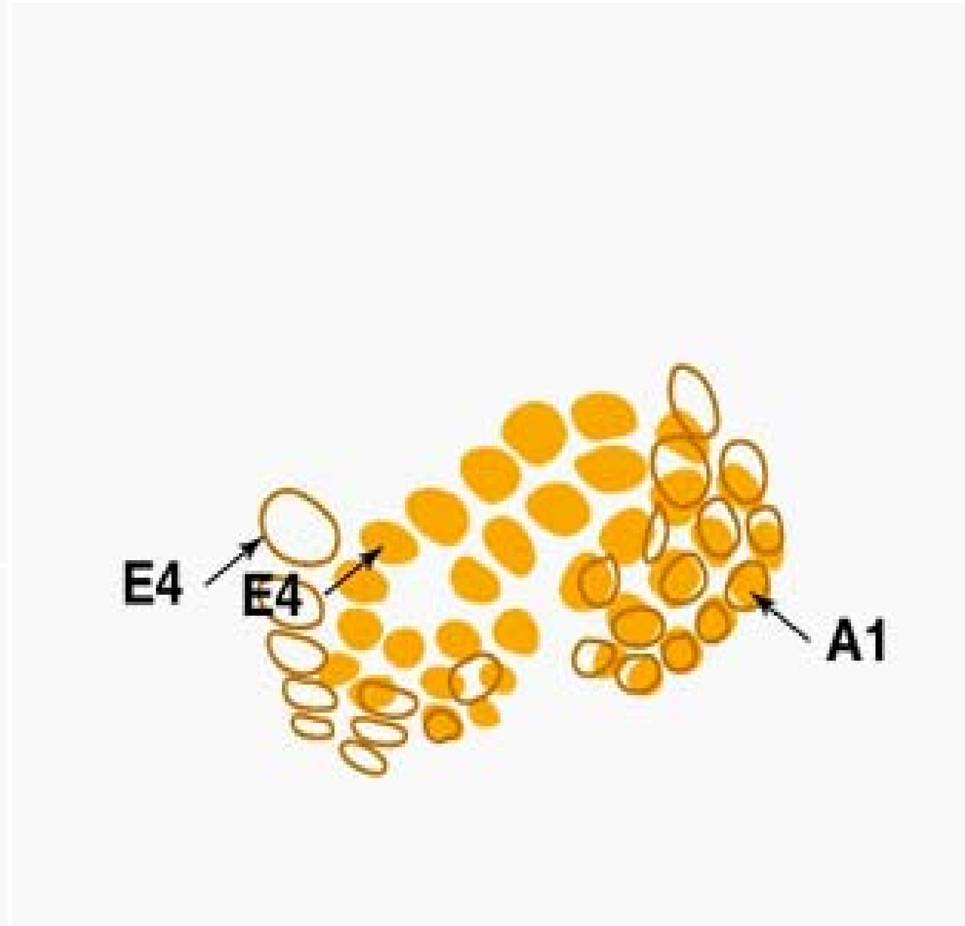
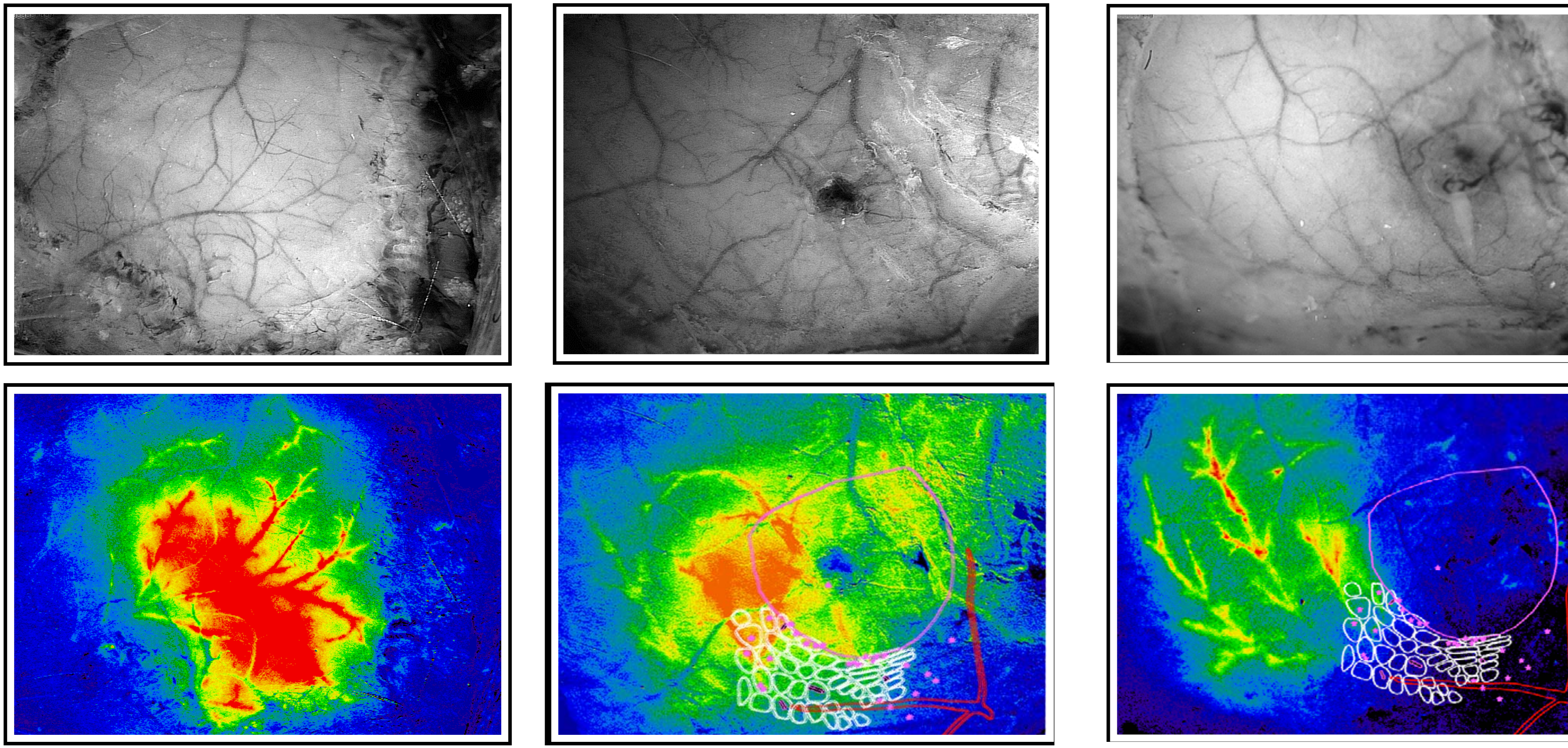

A1
A1


MCA
MCA
5 mm


E4
A1
1mm

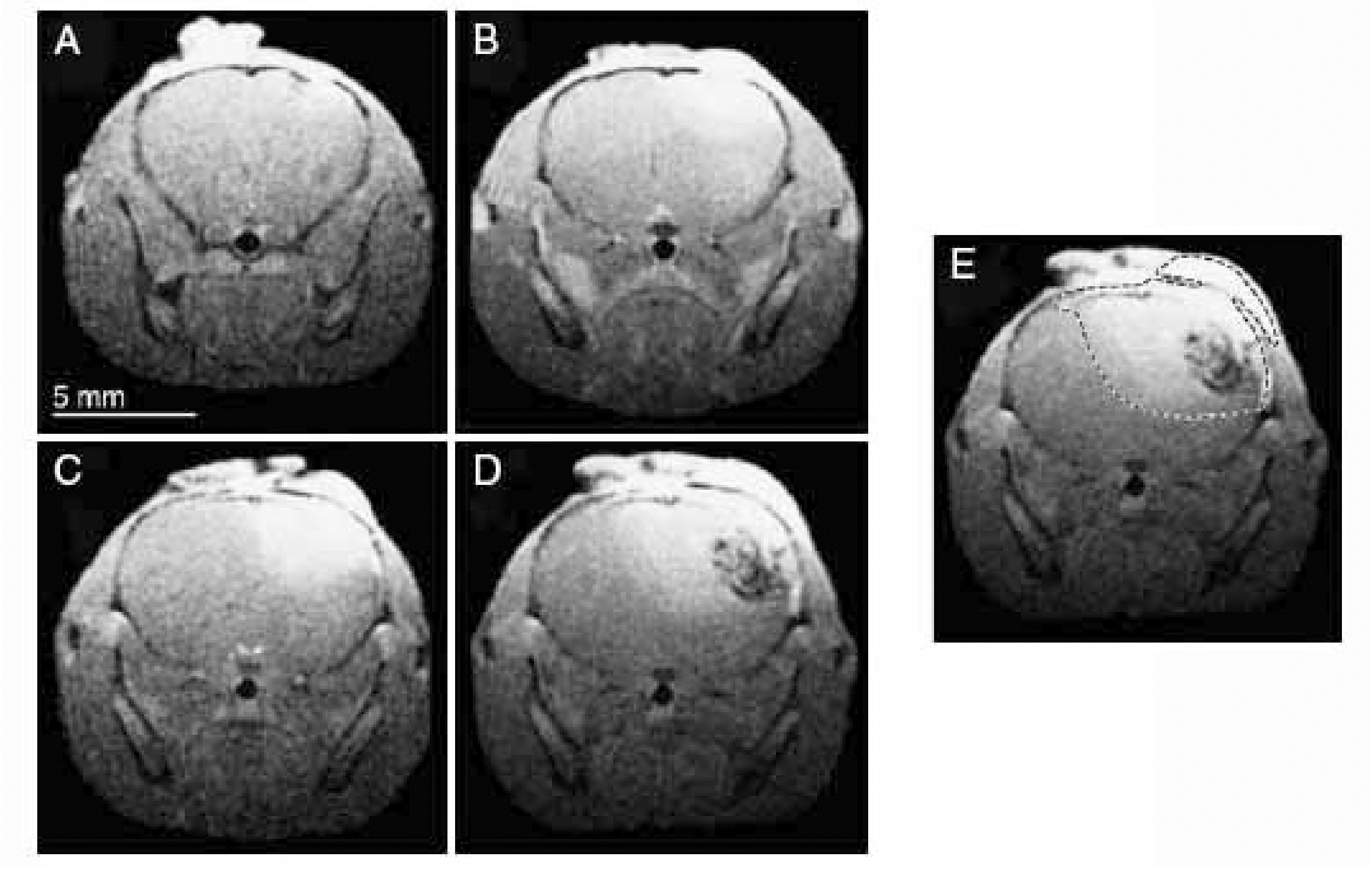

MRI
*
E4
A1

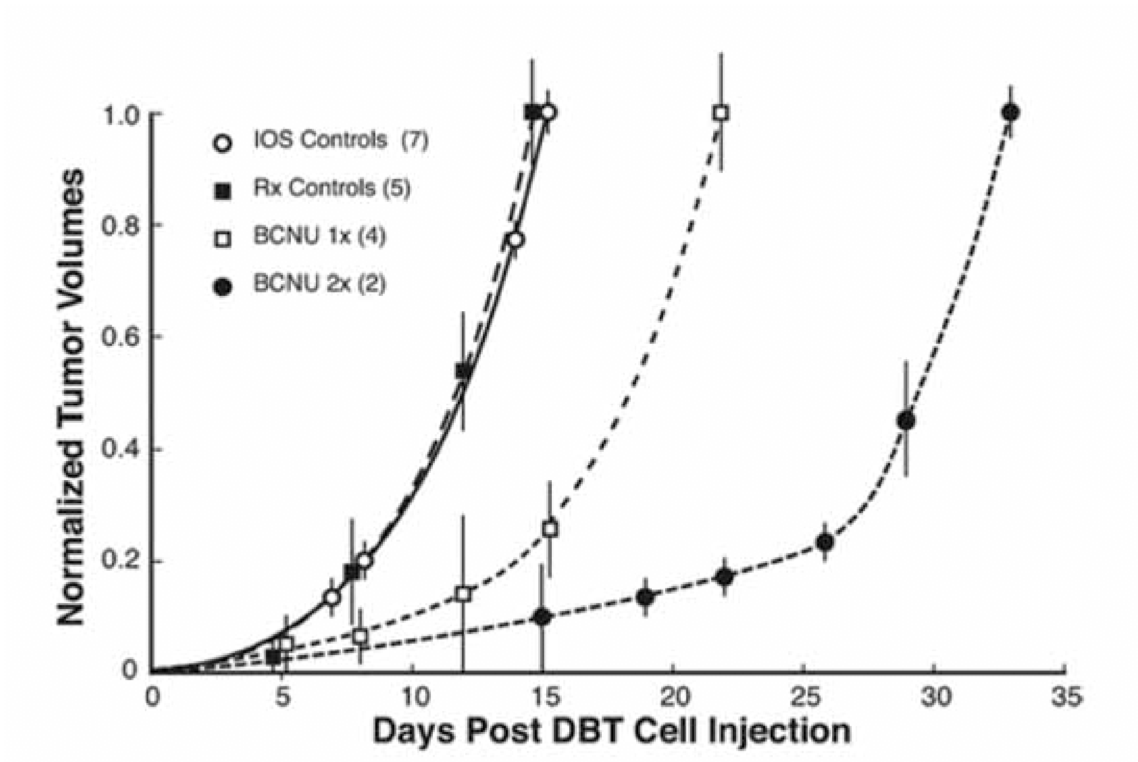

E4
E4
A1



Glioma 7 days

Glioma 15 days


A
B
C
D
E
5 mm


IOS Controls (7)
Rx Controls (5)
BCNU 1x (4)
BCNU 2x (2)
Normalized Tumor Volumes
Days Post DBT Cell Injection
0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
25
30
35

References - Cancer

Sherburn EW, Wanebo JE, Kim P, Song SK, Chicoine MR, Woolsey TA 1999 Gliomas in rodent whisker barrel cortex: a new tumor model. J Neurosurg *91*:814-821.

Jost SC, Wanebo JE, Song SK, Chicoine MR, Rich KM, Woolsey TA, Lewis JS, Mach RH, Xu J, Garbow JR 2007 *In Vivo* imaging in a murine model of glioblastoma. Neurosurgery *60:*360–371

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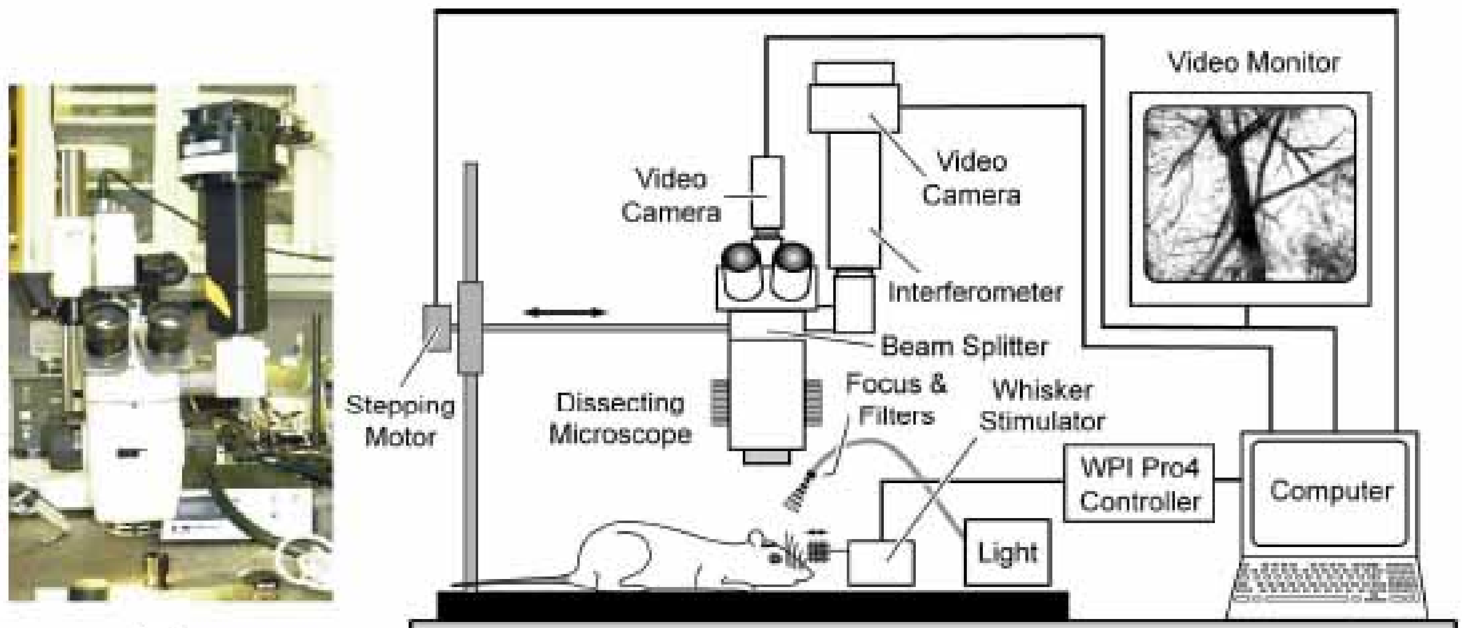
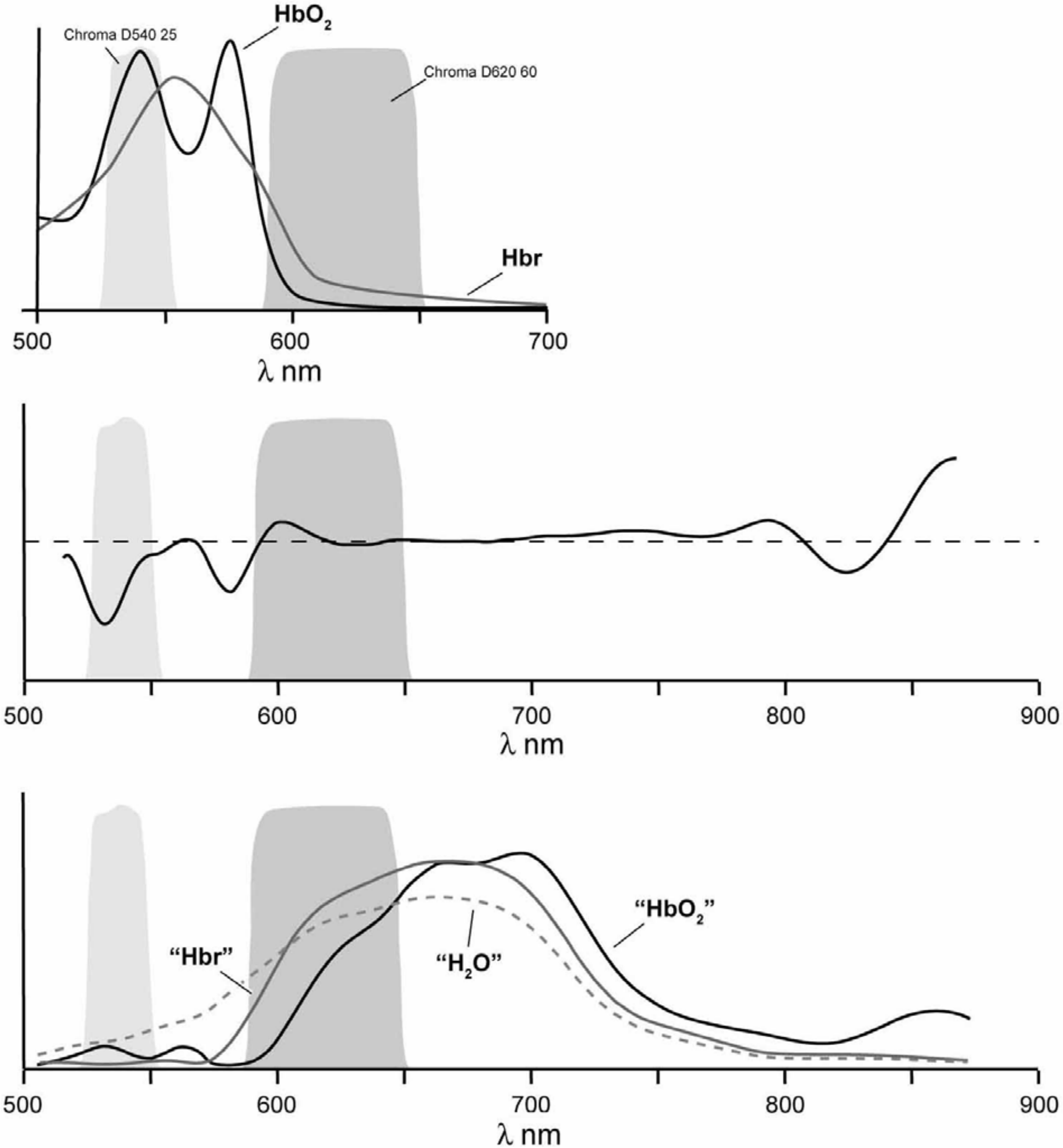

Video Monitor
Video Camera
Video Camera
Interferometer
Beam Splitter
Stepping Motor
Dissecting Microscope
Focus & Filters
Whisker Stimulator
WPI Pro4 Controller
Computer
Light

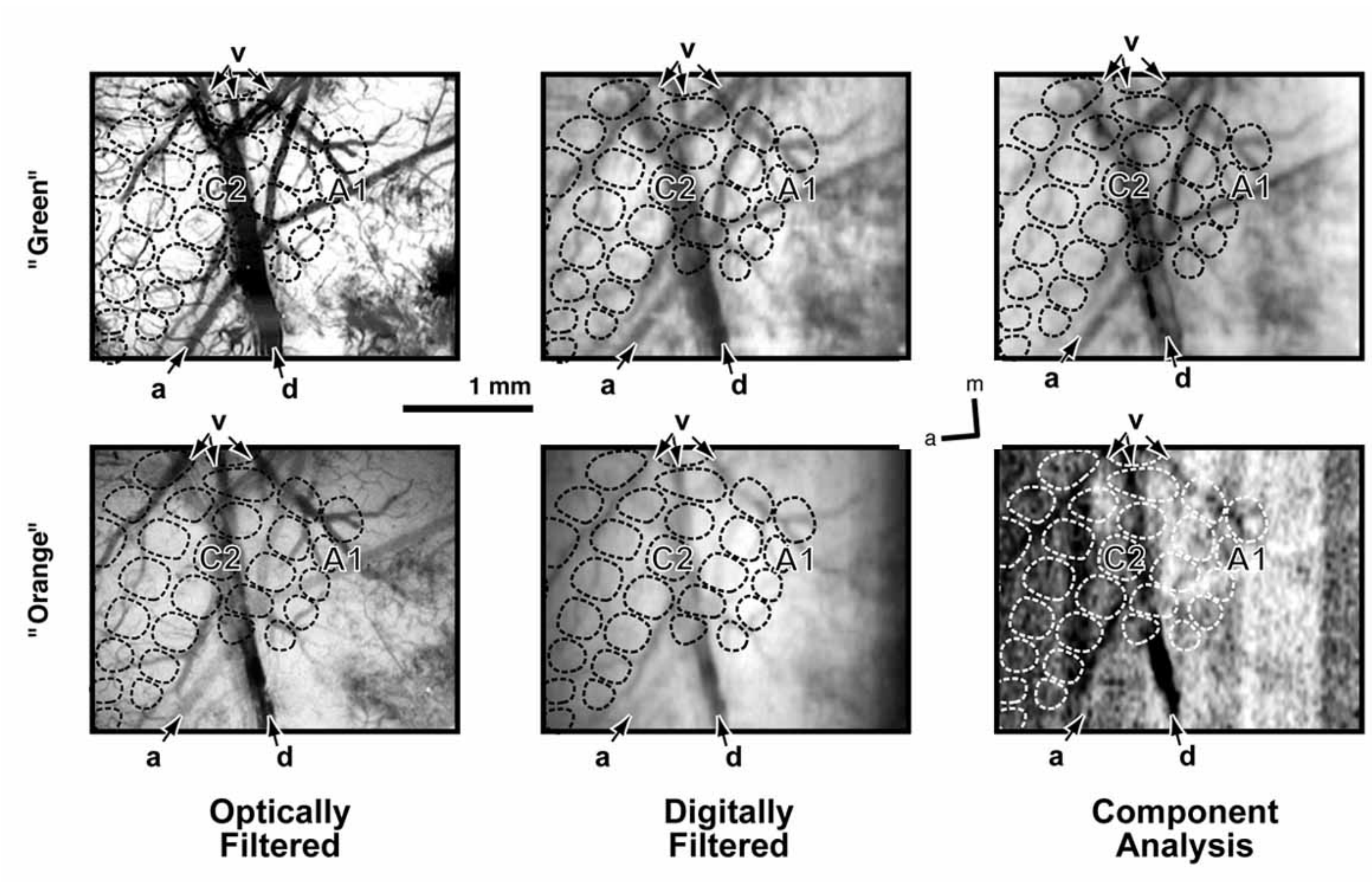
(a)

(b)



Septer

Disease


"Green"
"Orange"
v
C2
A1
a
d
1 mm
m
Optically Filtered
Digitally Filtered
Component Analysis

References - New Approach(es)

Adzamli K, Yablonskiy DA, Chicoine M, Won EK, Galen KP, Zahner M, Ackerman JJH, Woolsey TA 2003 Albumin-binding MR blood pool agents (MP-2269 and MS-325) as contrast agents in DBT intracranial mouse glioma model. MRM *49*:586-590.

Fox DJ Jr, Tysver Velde H, Preza C, O'Sullivan JA, Smith WH, Woolsey TA 2006 Computational hyperspectral interferometry for studies of brain function: proof of concept. Appl Opt *45*:3009-21.

Extracted from studies with colleagues in Anatomy and Neurobiology, Cell Biology and Physiology, Chemistry, Earth and Planetary Sciences, Electrical and Systems Engineering, Neurology, Neurosurgery, Pathology and Radiology at Washington University and at other organizations:

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Joel R. Garbow PhD

Roger M. Harris PhD

Yasuo Ido MD/DPhil

Sarah C. Jost MD

Yuri E. Moskalenko, PhD

Chrysanthe Preza DSc

Carl M. Rovainen, PhD

Joseph A. O'Sullivan PhD

Eric W. Sherburn MD

William H. Smith PhD

Sheng-Kwei Song PhD

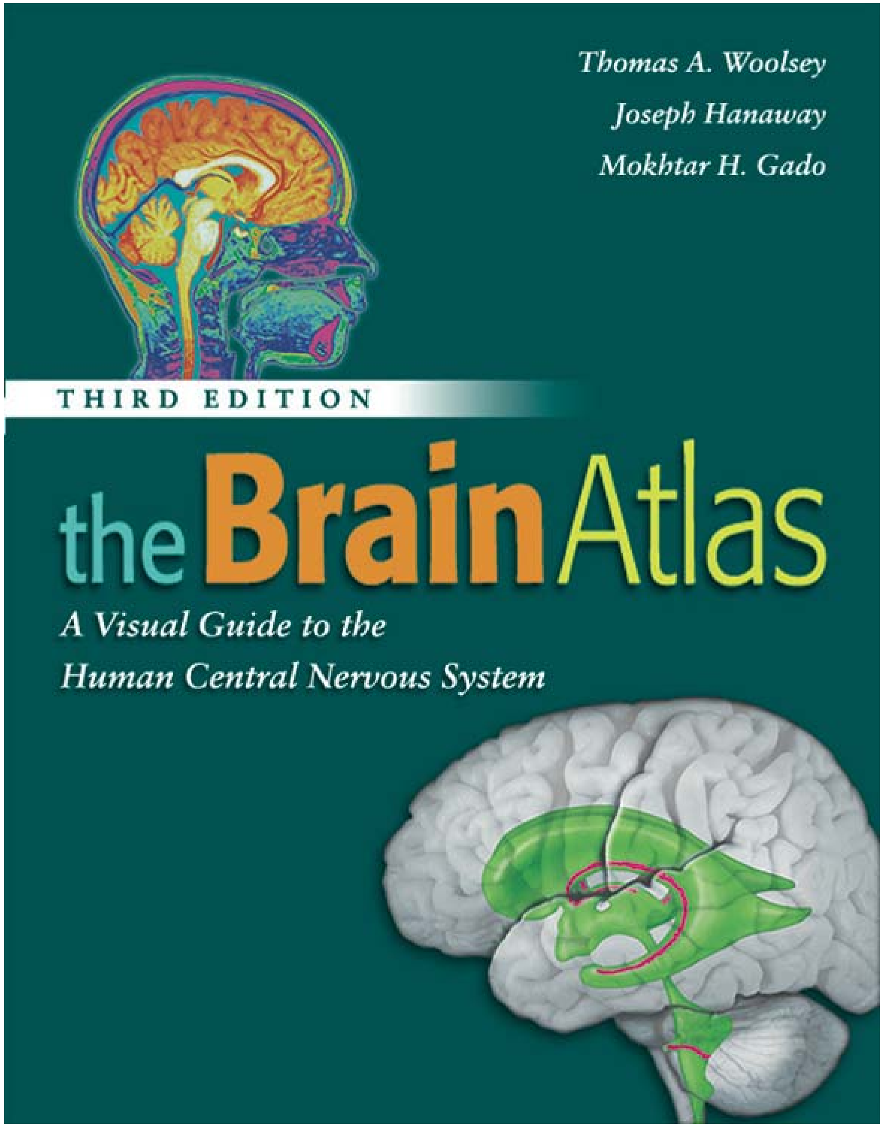
John E. Wanebo MD

Donald F. Wann DSc

Ling Wei MD

Joseph R. Williamson MD

Supported in part by: NIH 2P01NS049048, The McDonnell Center for Higher Brain Function and The Spastic Paralysis Foundation of the Illinois-Eastern Iowa District of the Kiwanis International



Thomas A. Woolsey
Joseph Hanaway
Mokhtar H. Gado
THIRD EDITION
the Brain Atlas
A Visual Guide to the
Human Central Nervous System

END

Cellular MRI for the Detection of Glioma

Ali S Arbab

Radiology
Henry Ford Health System
Detroit, Michigan

Background

Glioma typically exhibits hypervascularity and marked heterogeneity. Post contrast MRI or CT show enhancement due to vascular permeability, but both radiation necrosis and surgical trauma can show similar enhancement. However, active angiogenesis is only observed in tumor or recurrent tumor sites. This site of active angiogenesis can be exploited to identify tumor.

Dendritic cell based vaccination treatment is under clinical trial. There are evidences showing accumulation of cytotoxic T-lymphocytes (CTL) sensitized by glioma-cell lysate pulsed dendritic cell at the site of glioma recurrence. These sensitized T-cell might not show any affinity towards the site of radiation necrosis or surgical trauma. This immunogenic reaction can be exploited to identify tumor.

Purposes

To determine whether magnetically labeled endothelial progenitor cells (EPC) can be used to identify glioma and differentiate glioma from radiation necrosis on the basis of active angiogenesis.

To determine whether magnetically labeled CTL can be used to identify glioma on the basis of active immunogenic reaction.

Materials

Cells:

Cord blood endothelial progenitor cells (EPCs, AC133+ cells)
Sensitized splenocytes from gliosarcoma (9L) bearing rats
Human glioma cell line (U251)
Rat gliosarcoma cell line (9L)

Animals:

Nude rats for human glioma (U251) tumor and radiation injury
Fisher 344 rats for rat gliosarcoma (9L) tumor

SPIO:

Ferumoxides (Feridex, 100 µg/ml/4 million cells)

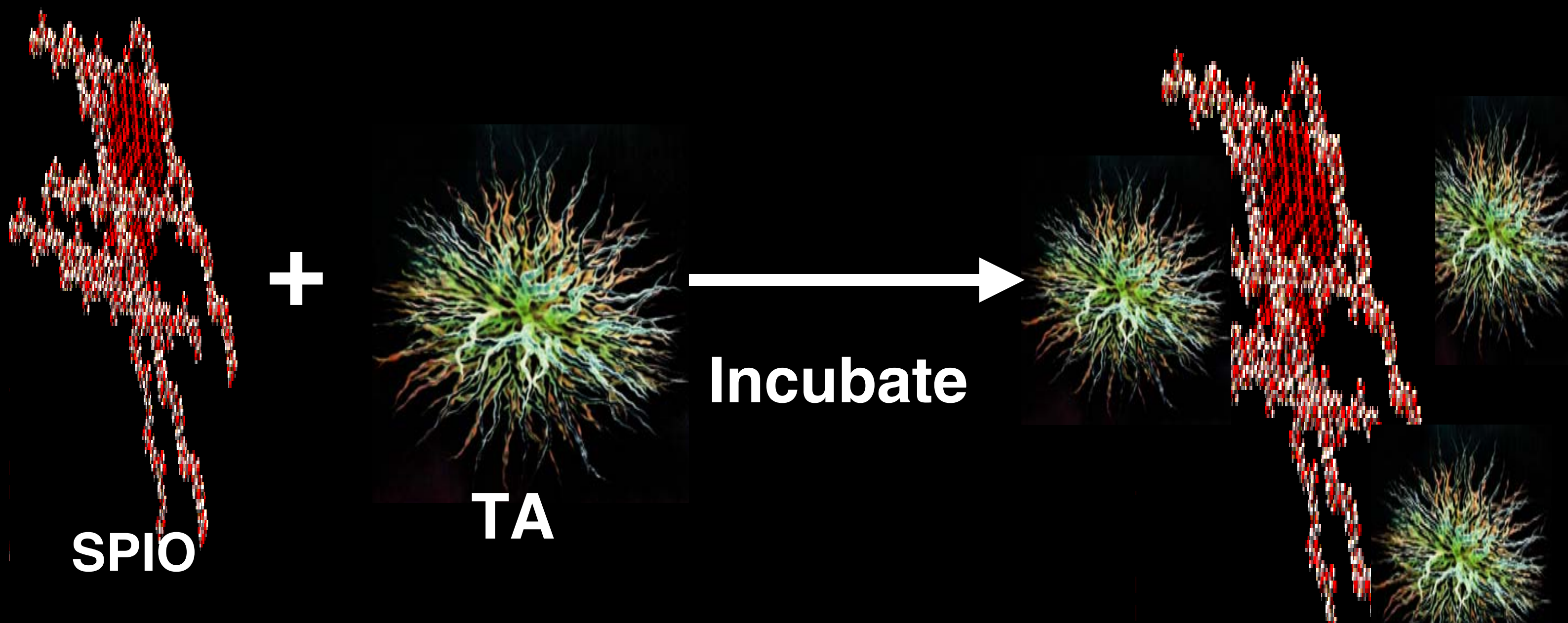
Transfection agent:

Protamine sulfate (4 µg/ml/4 million cells)

MRI:

7 Tesla system with Bruker advanced console

Transfection agents mediated



Zeta Potential for SPIO

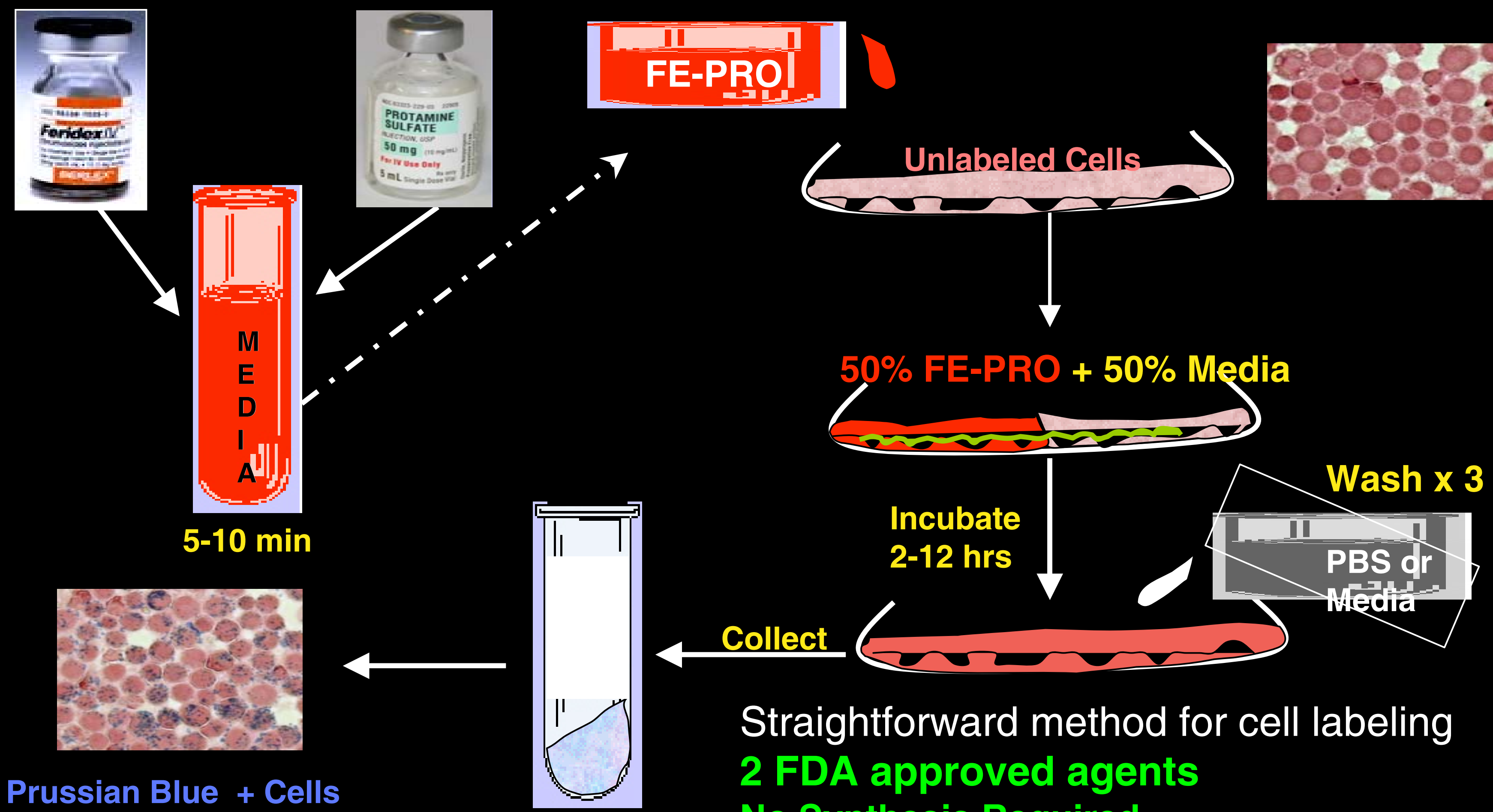
MION-46L	- 2.03 ± 0.39 mv
Feridex	- 41.3 ± 0.98 mv

Zeta Potential for TA

Superfect	1.0 ± 2.50 mv
Polyfect	19.1 ± 1.01 mv
Poly-L-Lysine	30.1 ± 17.8 mv
Plus	27.1 ± 1.22 mv
Lipofectamine	65.3 ± 5.22 mv
Protamine Sulfate	7.1 ± 0.01 mv

Electrostatic Interaction between Dextran Coated Superparamagnetic Iron Oxide Nanoparticles and Transfection Agents

Cell labeling



Straightforward method for cell labeling

2 FDA approved agents

No Synthesis Required

High Labeling Efficiency

Protamine Sulfate: FDA Approved (Heparin Antagonist),
<u>100x Transfection Efficiency compared to PLL#</u>, LD_{50} = 100 mg/kg, Assay using PTT.

Sorgi FL et al Gene Therapy 1997;4:961, Arbab AS et al Blood, 2004

Methods

Acquisition of in vivo MRI:

Multiecho T2-weighted (TEs of 10, 20, 30, 40, 50 and 60 msec and a TR of 3000 msec, 32 mm FOV, 1 mm slice thickness, 256x256 matrix, and NEX = 2). Multiecho T2*-weighted (TEs of 5, 10, 15, 20, 25, and 30 msec and a TR of 3000 msec, 32 mm FOV, 1 mm slice thickness, 256x256 matrix, and NEX = 2) and 3D gradient echo (TR=100 msec, TE=9 msec, 10º flip angle, 32x24x16 mm^3 FOV, 256x192x128 matrix, and NEX = 1).

Histology and immunohistochemistry:

FITC labeled tomato lectin was used to identify endothelial lining

Prussian blue staining with or without DAB enhancement was performed to identify iron positive cells

Markers of endothelial cells were also identified by IHC

Tumor identification by EPC

Tumor implantation (U251)

↓ 7 Days

Labeling & IV injection of EPCs

↓ 7 Days

MRI & Euthanasia

Irradiation (75 Gy)

↓

Pre IV EPCs MRI
2, 4, 6 & 8 Weeks

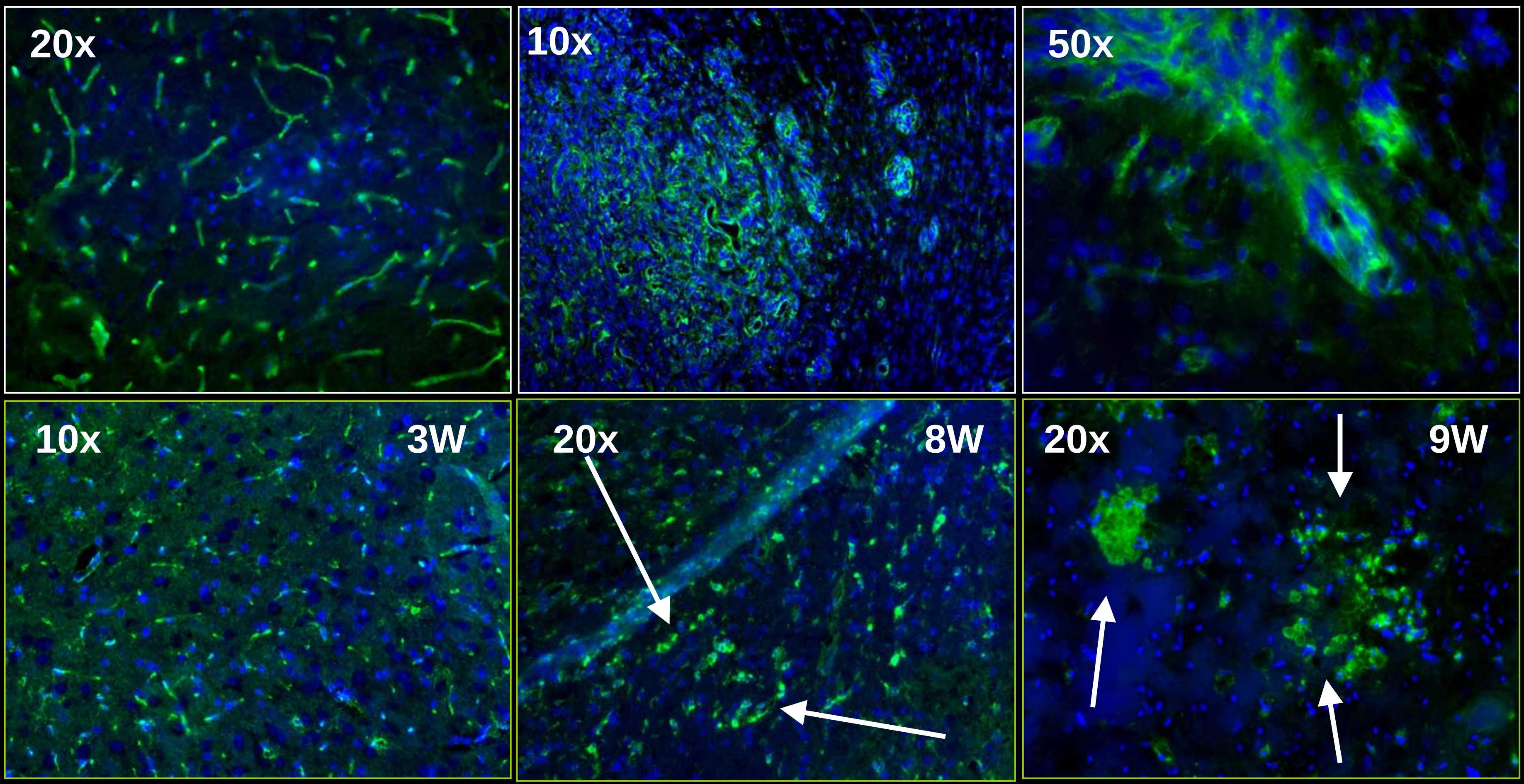
Labeling & IV injection of EPCs
2, 4, 6 & 8 Weeks

↓ 7 Days

Post IV EPCs MRI
3, 5, 7 & 9 Weeks & Euthanasia

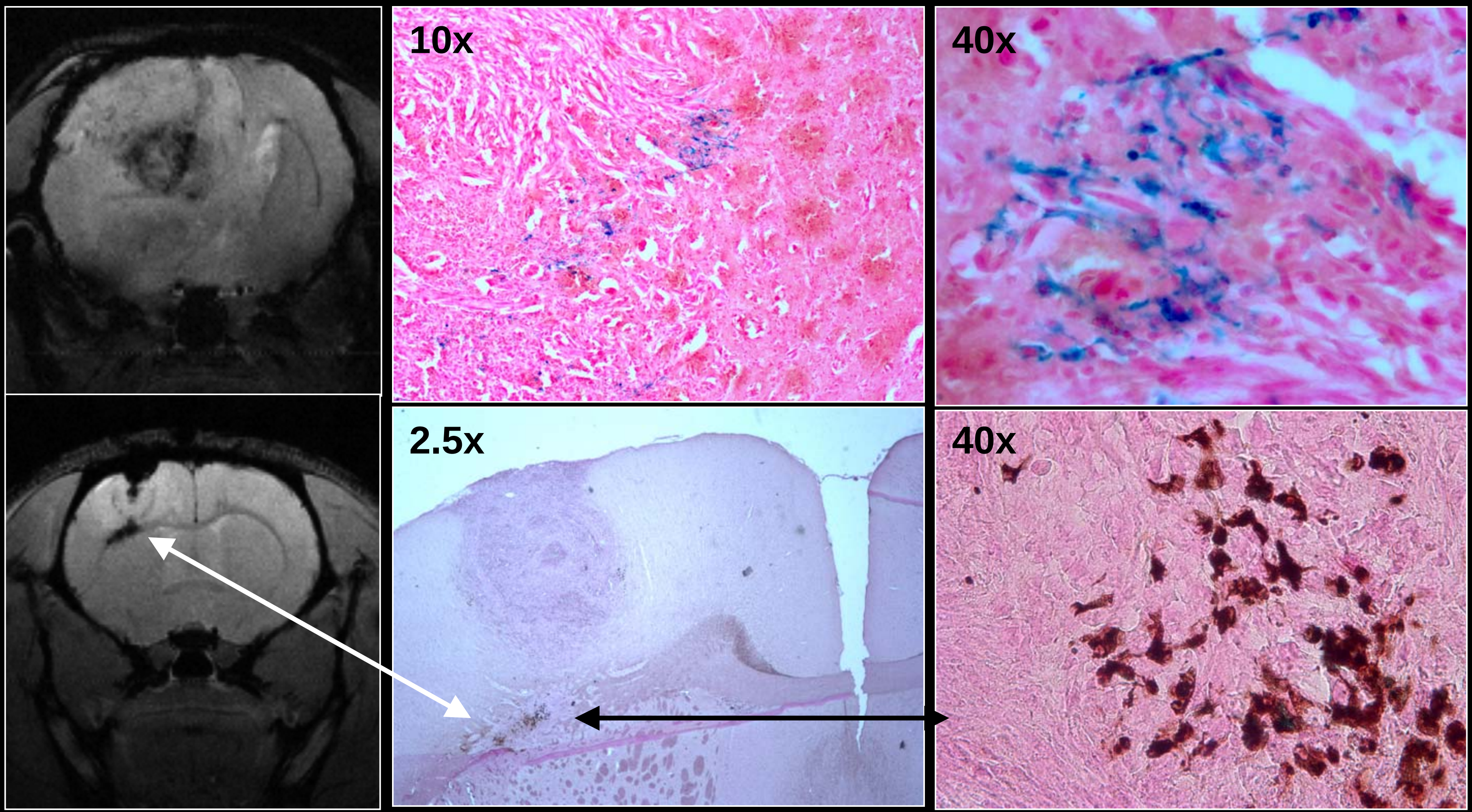
Results

Vascularity changes in tumor (upper row) after 14 days of implantation of U251 and after irradiation (lower row) at different intervals



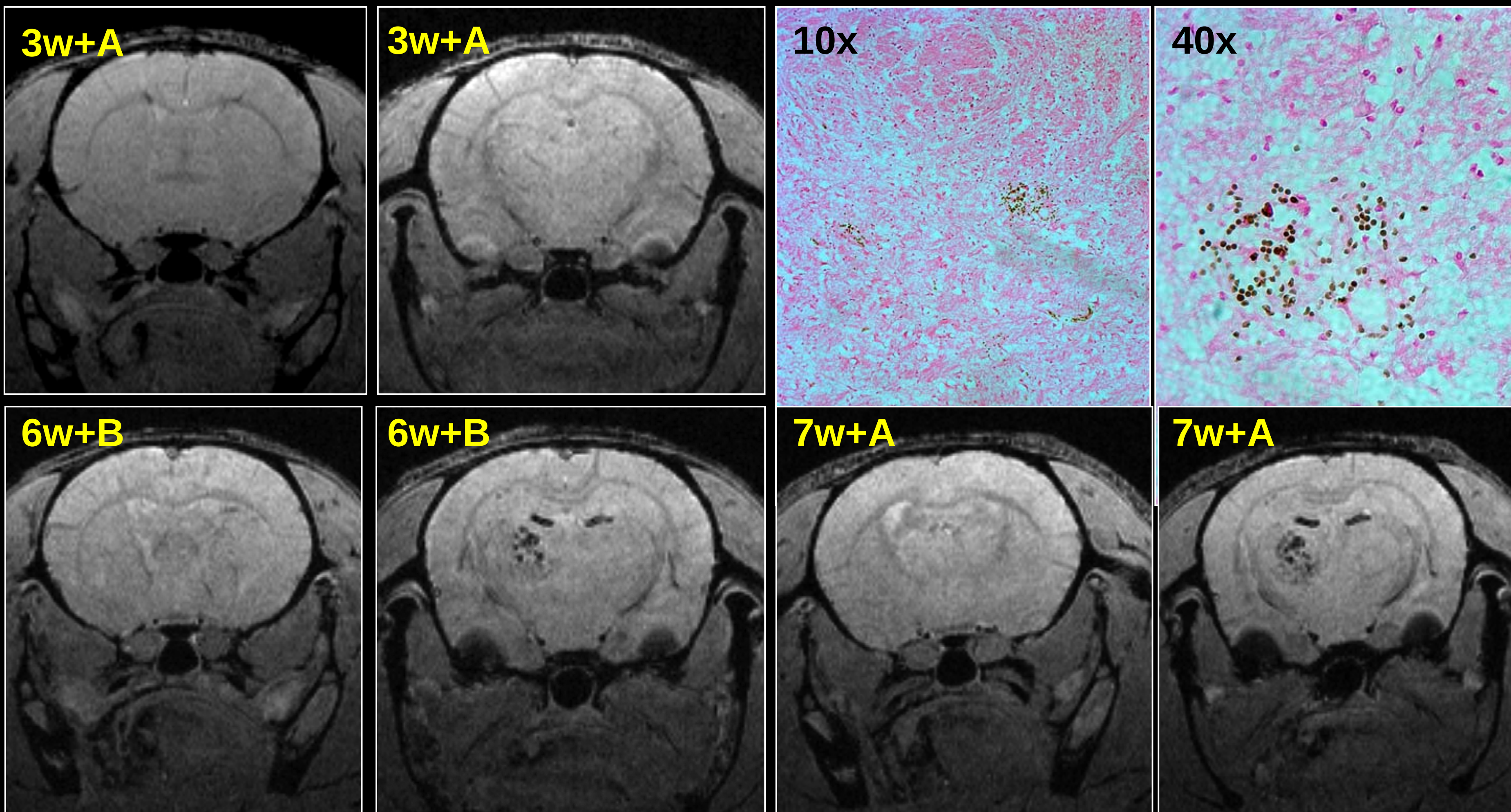
Results

Accumulation of labeled EPCs in U-251 tumors (left column) detected by *in vivo* MRI and corresponding Prussian blue staining (Middle and right columns)



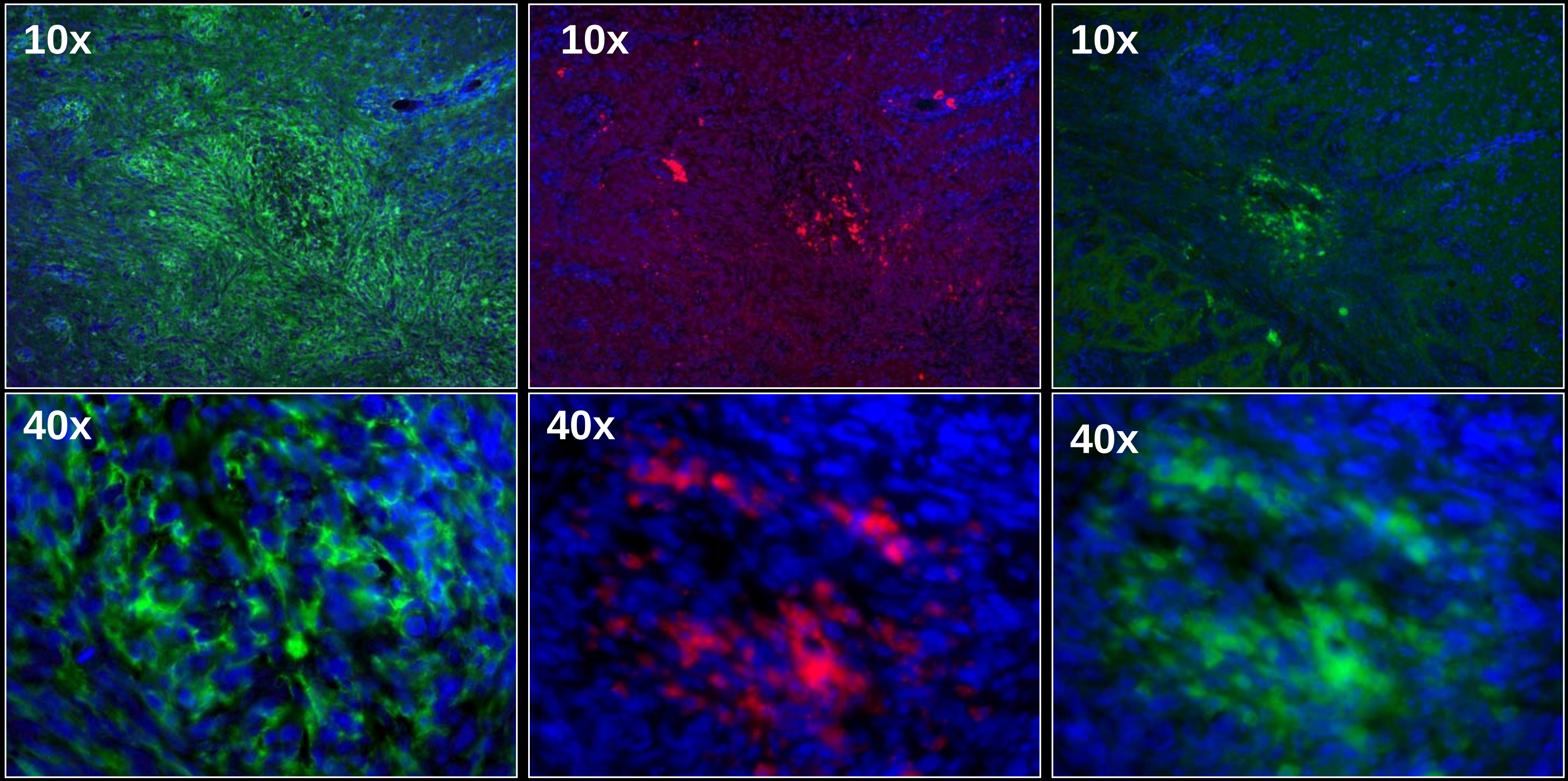
Results

MRI of Irradiated rat brains before and 7 days after administration of labeled EPCs and corresponding Prussian blue staining



Results

Expression of CD31 markers in administered EPCs that were accumulated at the site of tumor. Lectin positive cell lining (left), DiI positive cells (middle) and CD31 positive cells (right) at the corresponding sites



Tumor identification by CTL

Tumor implantation (9L)

10 Days

Collection of Splenocytes & Labeling

(from control and tumor bearing rats)

24 Hours

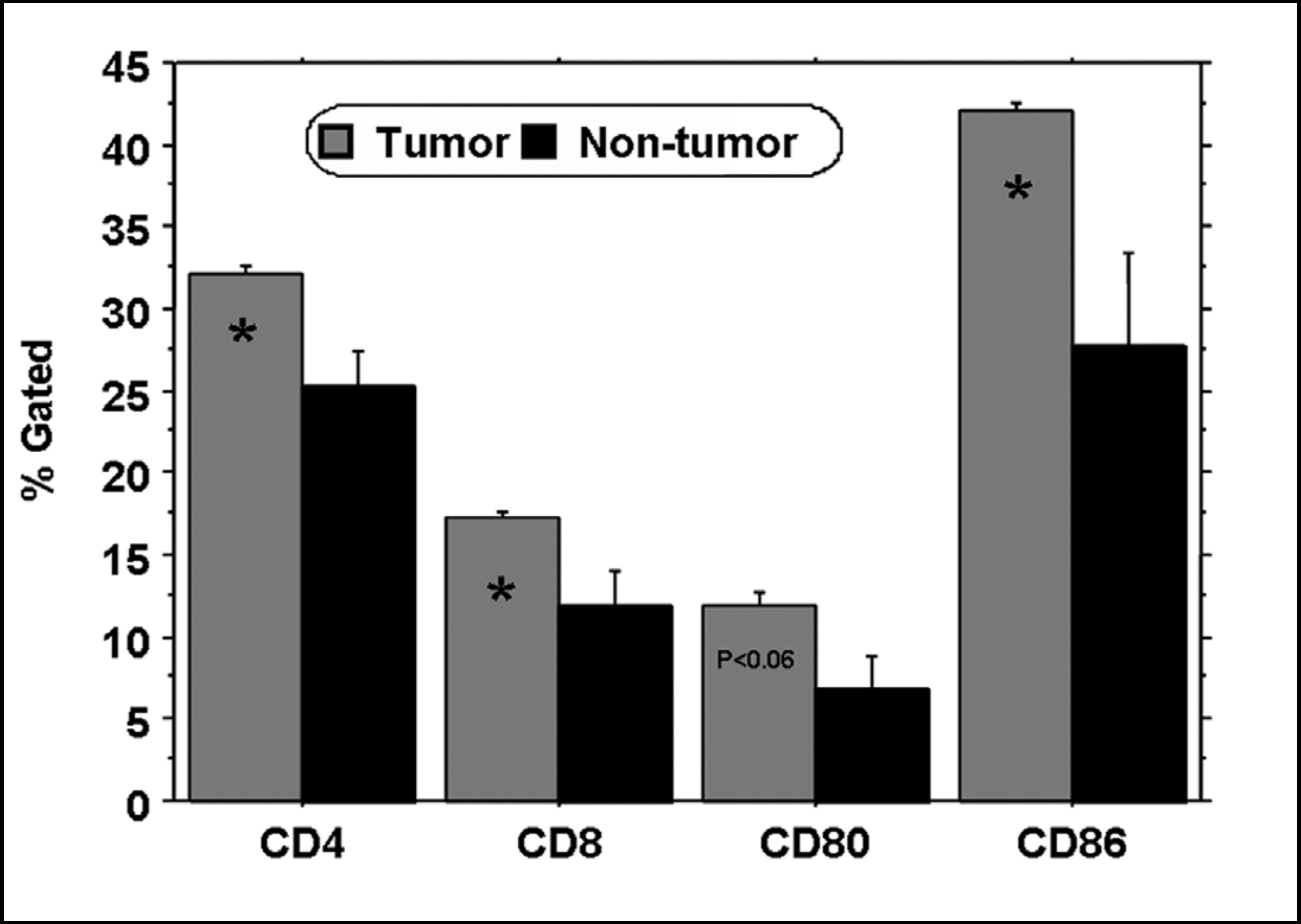
IV injection

72 Hours

MRI & Euthanasia

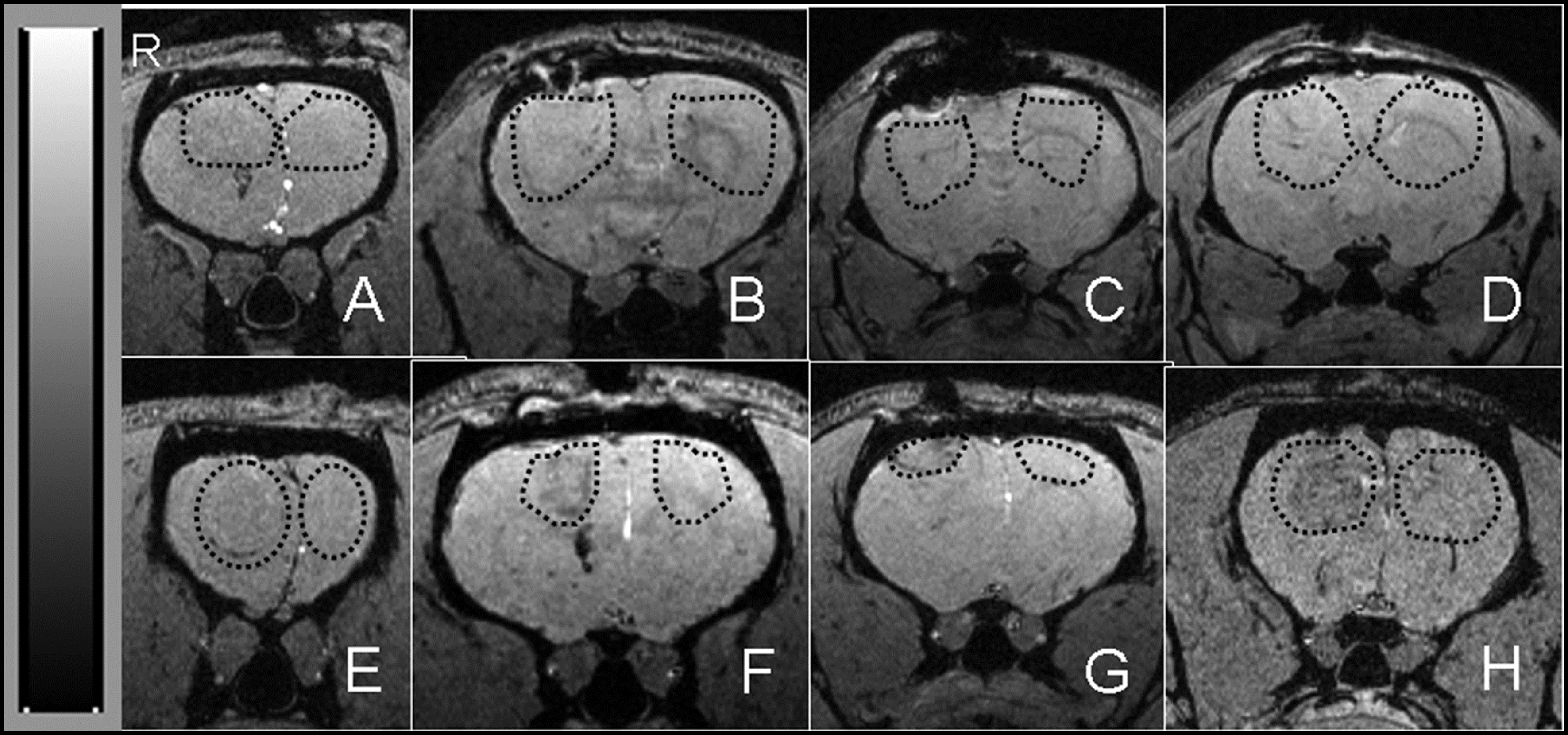
Results

Distribution of T-cells and antigen presenting cells population in control and sensitized splenocytes



Results

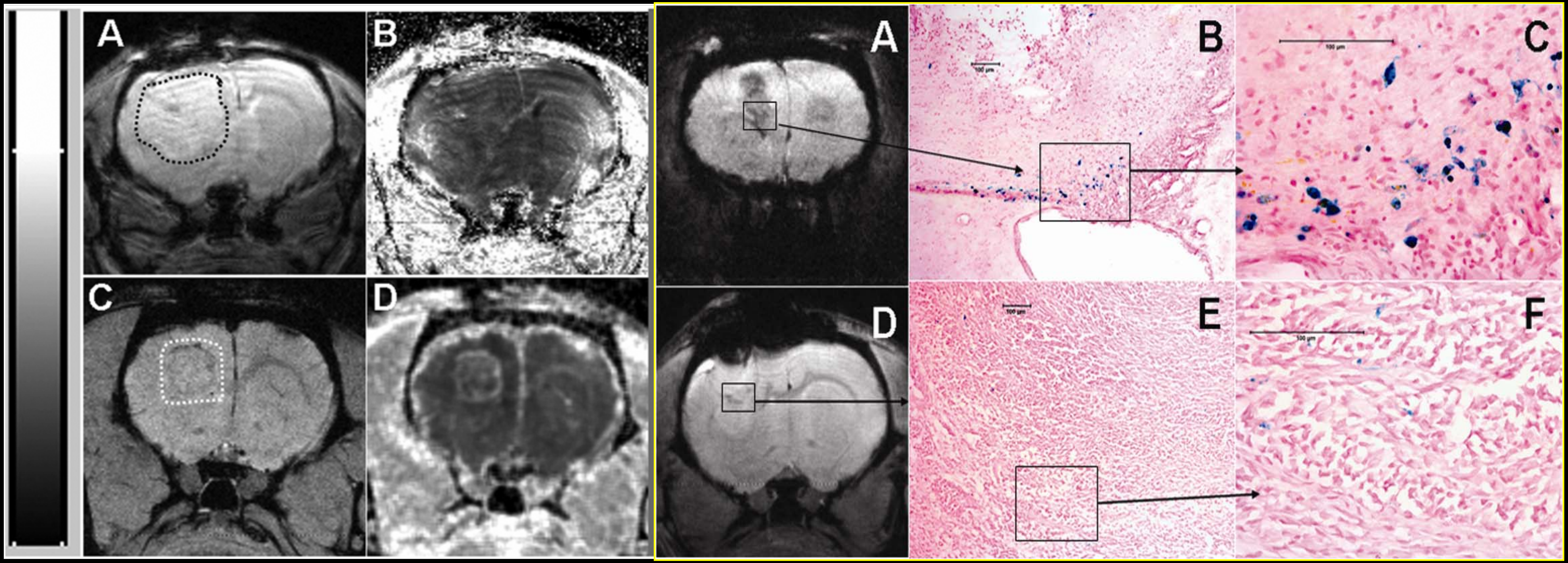
Representative sections of 3D GRE images from all rats that received control (upper row) and sensitized splenocytes (lower row)



Results

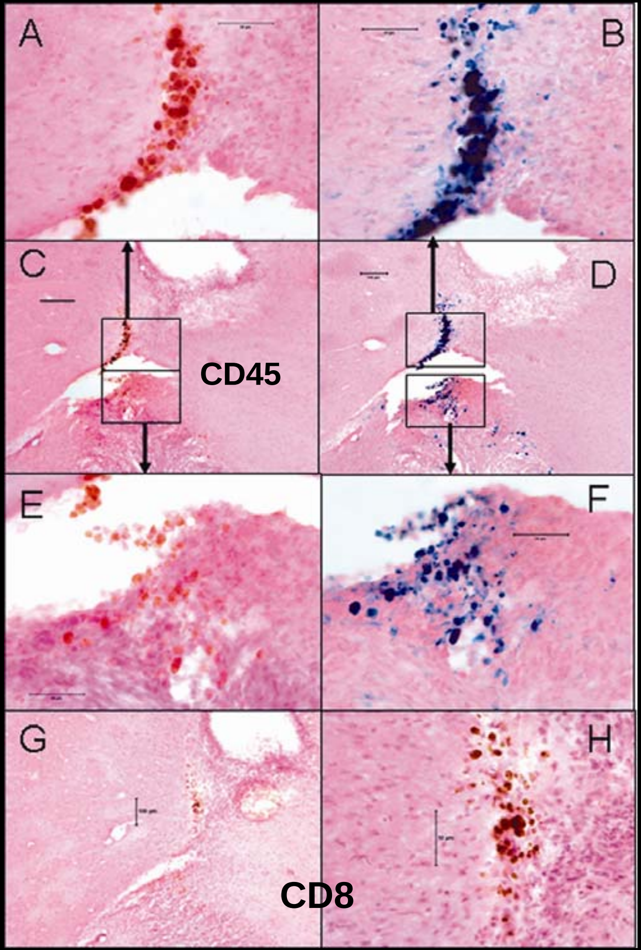
Representative T2*W images and corresponding R2*-maps from rats that received control (A,B on right panel) and sensitized splenocytes (C,D on right panel).

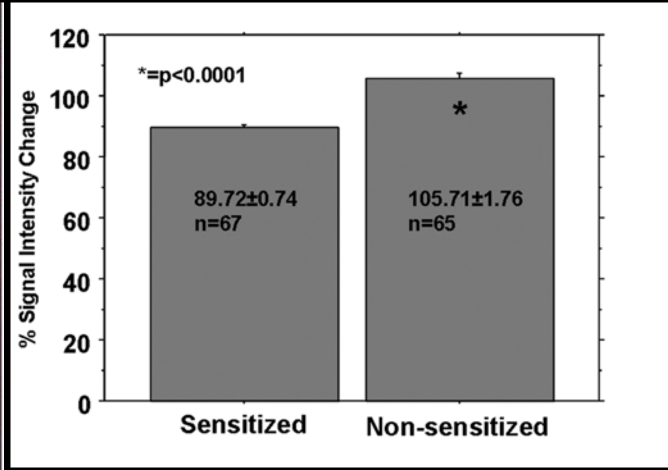
Left panel show representative T2*W images (TE = 10 ms) from rats that received control (lower row) and sensitized splenocytes (upper row) and corresponding Prussian blue stained sections.

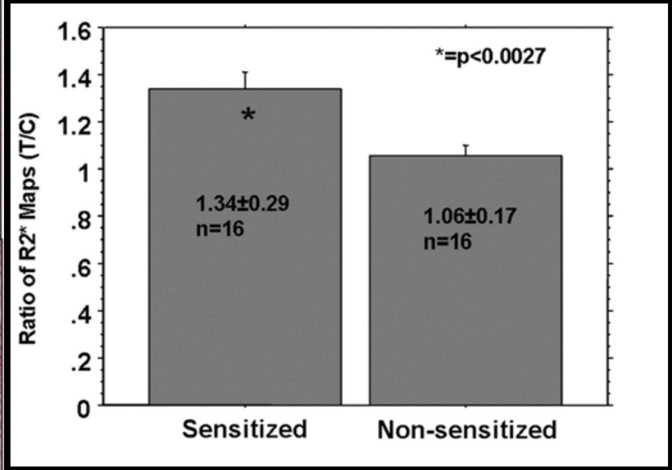


Results

Left panel: Immunohistochemistry and corresponding Prussian blue staining
Right panel: Signal intensity on 3D GRE (upper) and R2* values (lower) calculated from all sections.







Conclusion

Both EPCs and sensitized T-cells could be probes for in vivo cellular magnetic resonance (CMRI) imaging to identify glioma and to differentiate glioma from radiation necrosis

Acknowledgement

Radiology Research:

Dr. Hamid Soltanian-Zadeh
Dr. Ali M Rad,
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Dr. Guangliang Ding

Radiology Oncology:

Dr. Steve Brown

ENS/CC/NIH:

Dr. Joe Frank

Thank You

MRI-guided transplantation of neural stem cells in stroke.

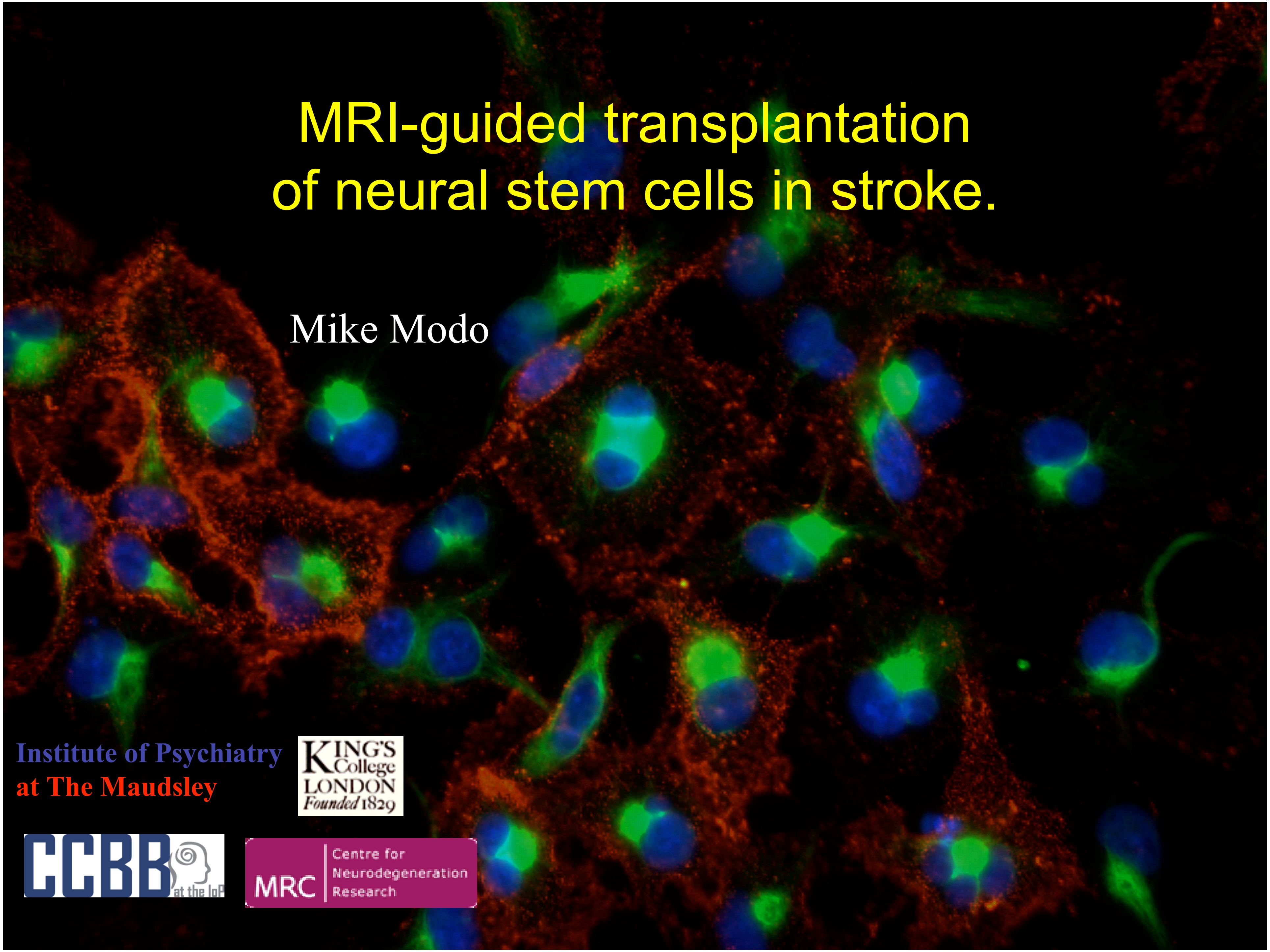
Mike Modo

Institute of Psychiatry
at The Maudsley

KING'S College LONDON Founded 1829

CCBB at the IoP

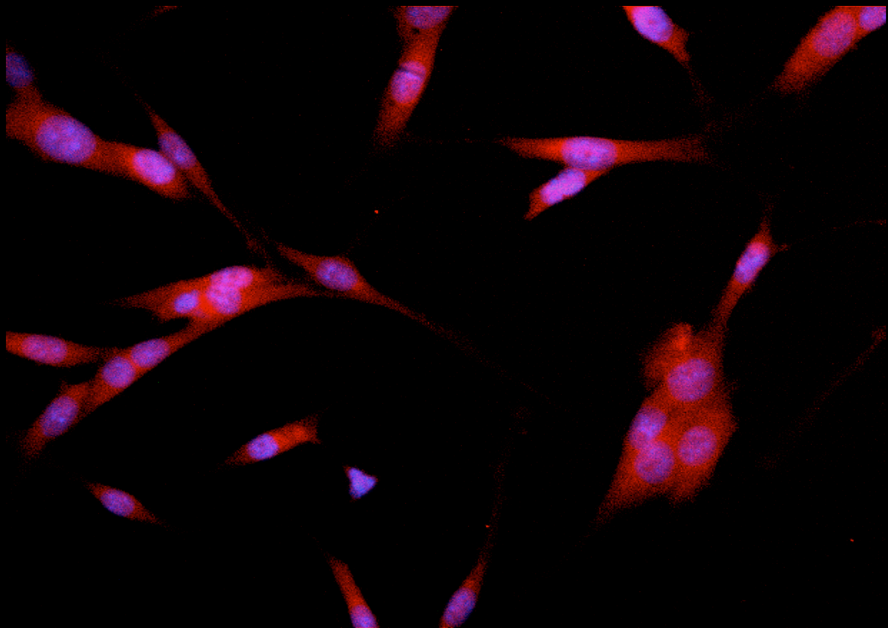
MRC Centre for Neurodegeneration Research

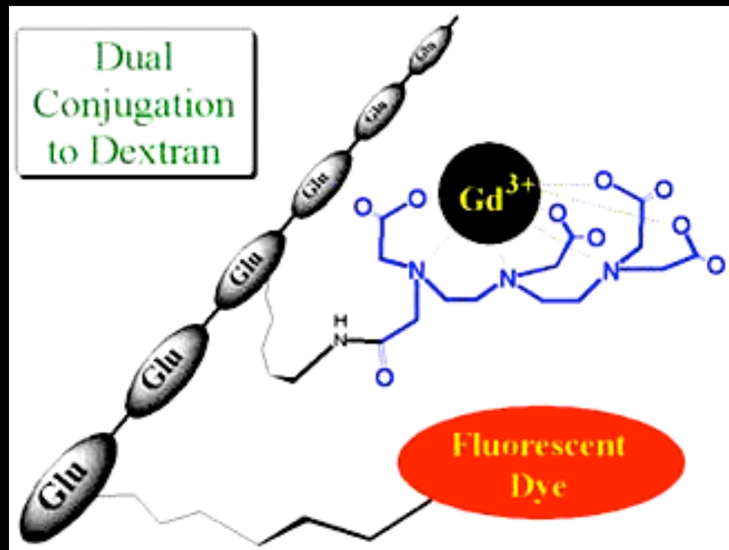


In vitro pre-labelling

Bimodal Contrast Agent:

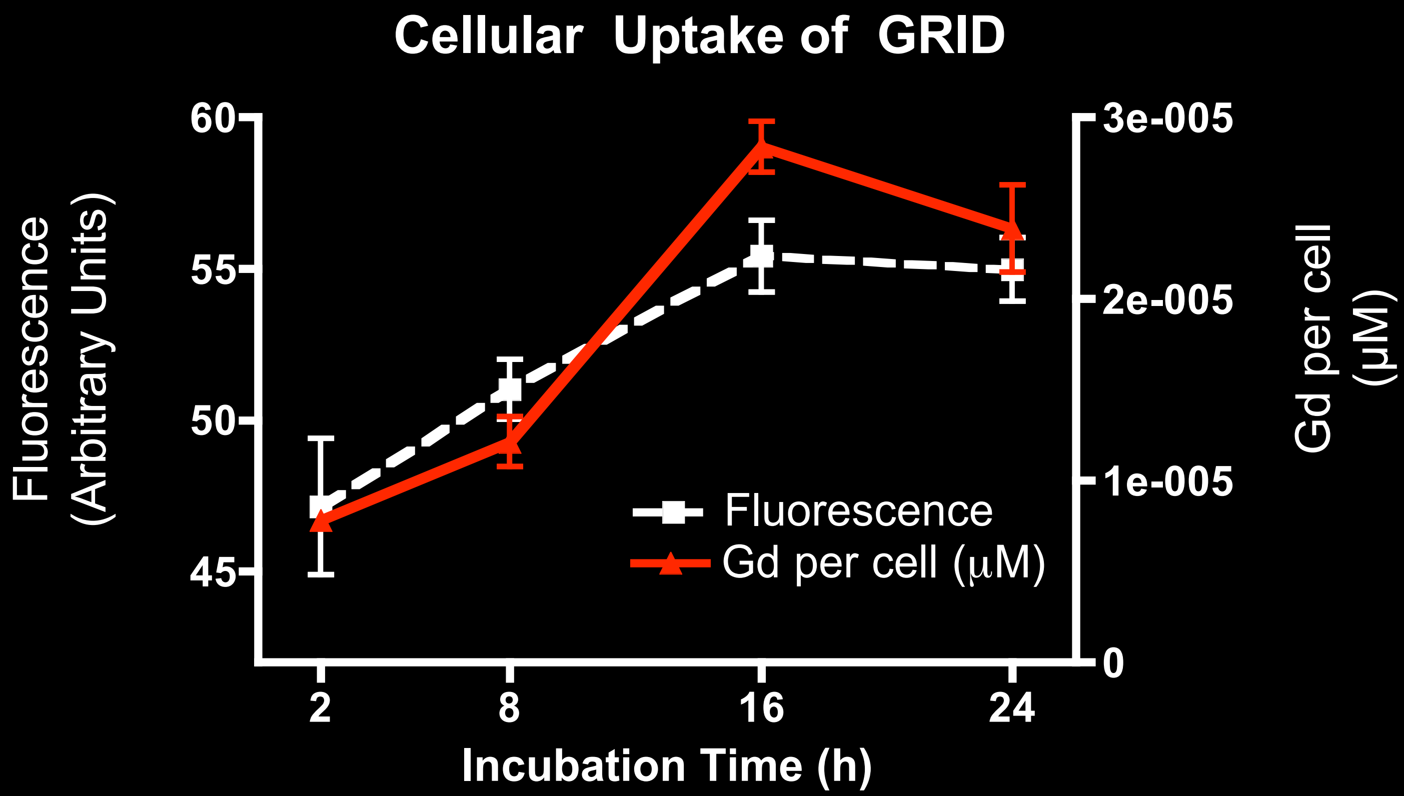
Detectable by both MRI and fluorescent microscopy



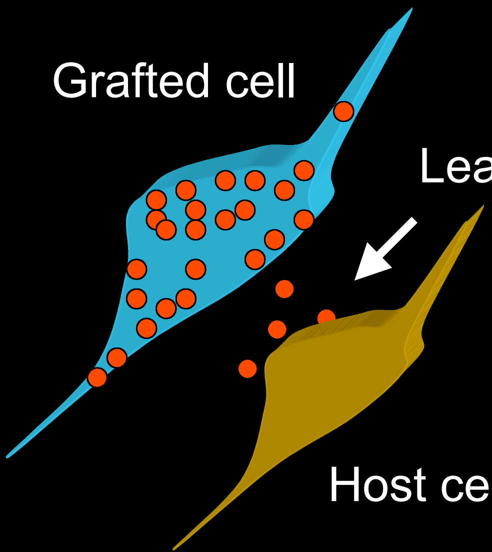


GRID: ***G***adolinium ***R***hodam***I***ne ***D***extran

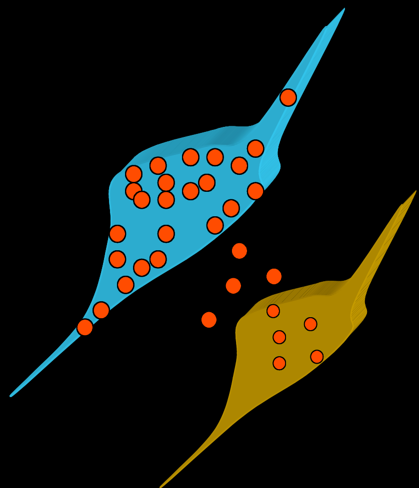
Quantification of cell uptake



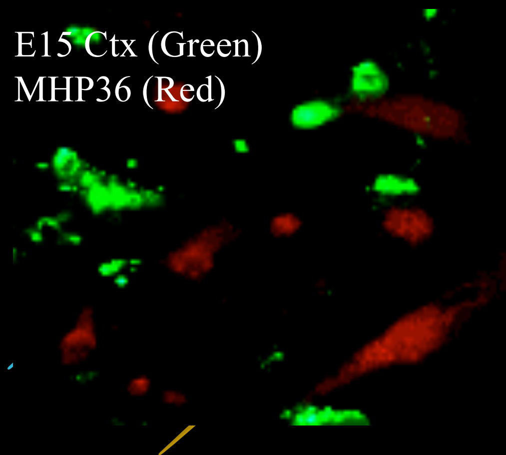
Leakage & Re-uptake of contrast agent: Possible source of false positives



1. Uptake → False Positive



2. No Re-Uptake → Selective Detection

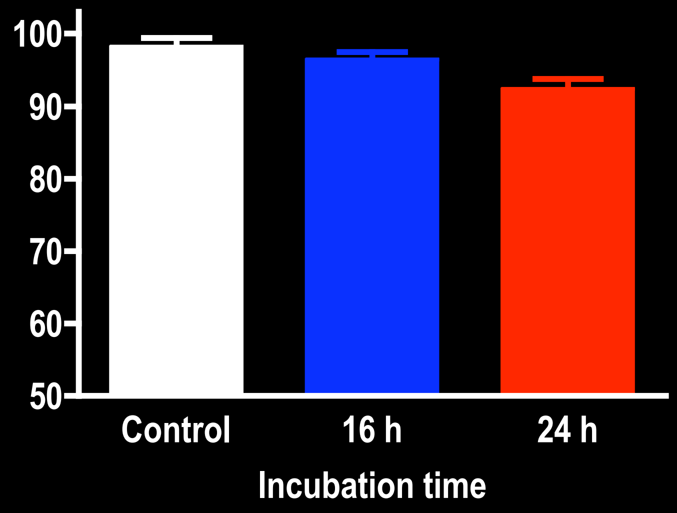


No leakage or re-uptake in co-culture

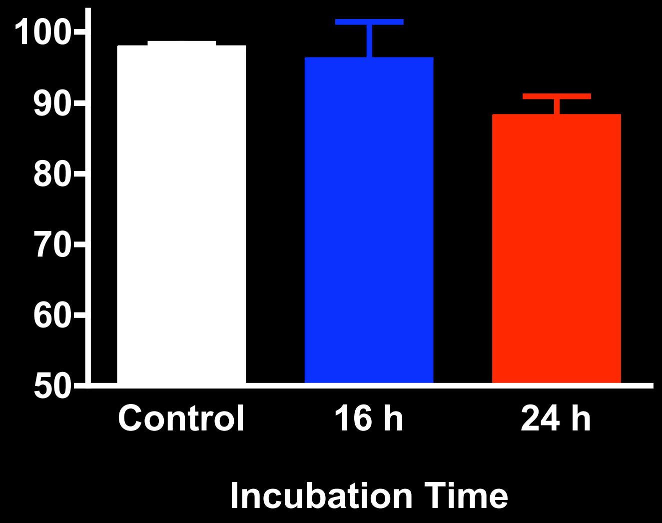
Modo et al (2002) Neuroimage

In vitro effects on cell viability

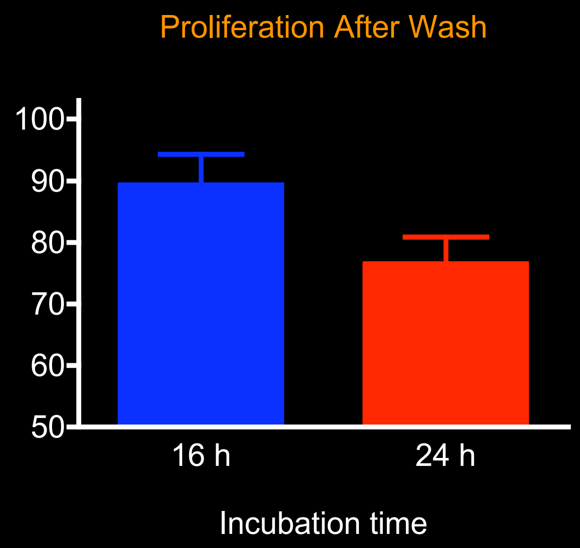
Viability After Wash

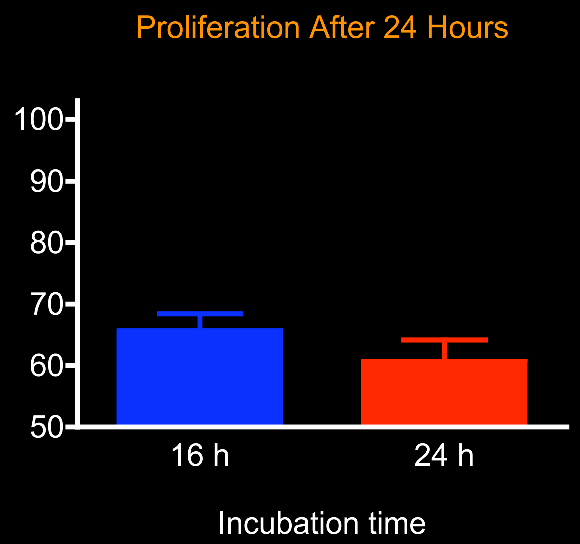


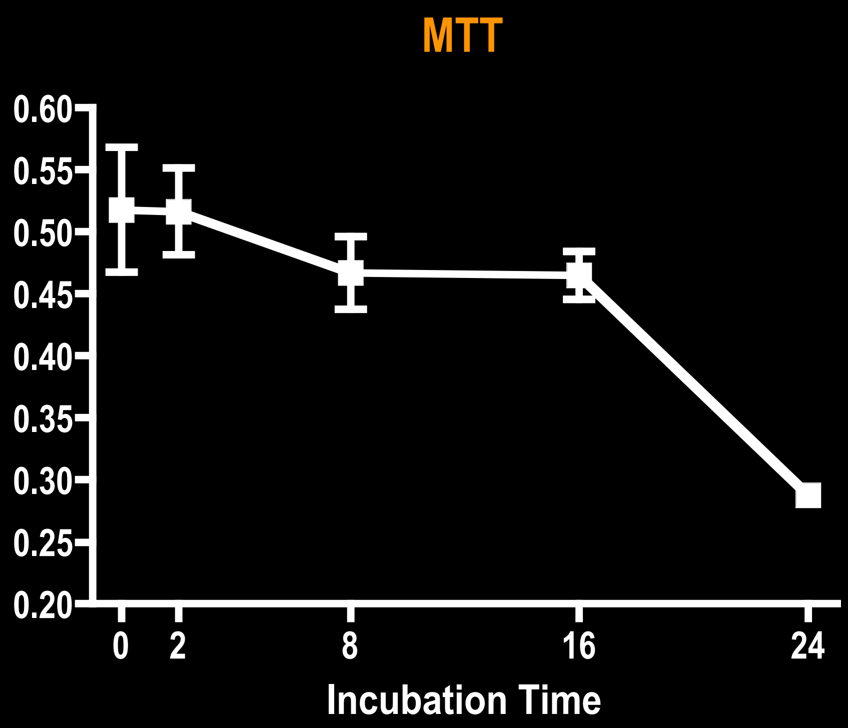
Viability After 24 Hours



Proliferation



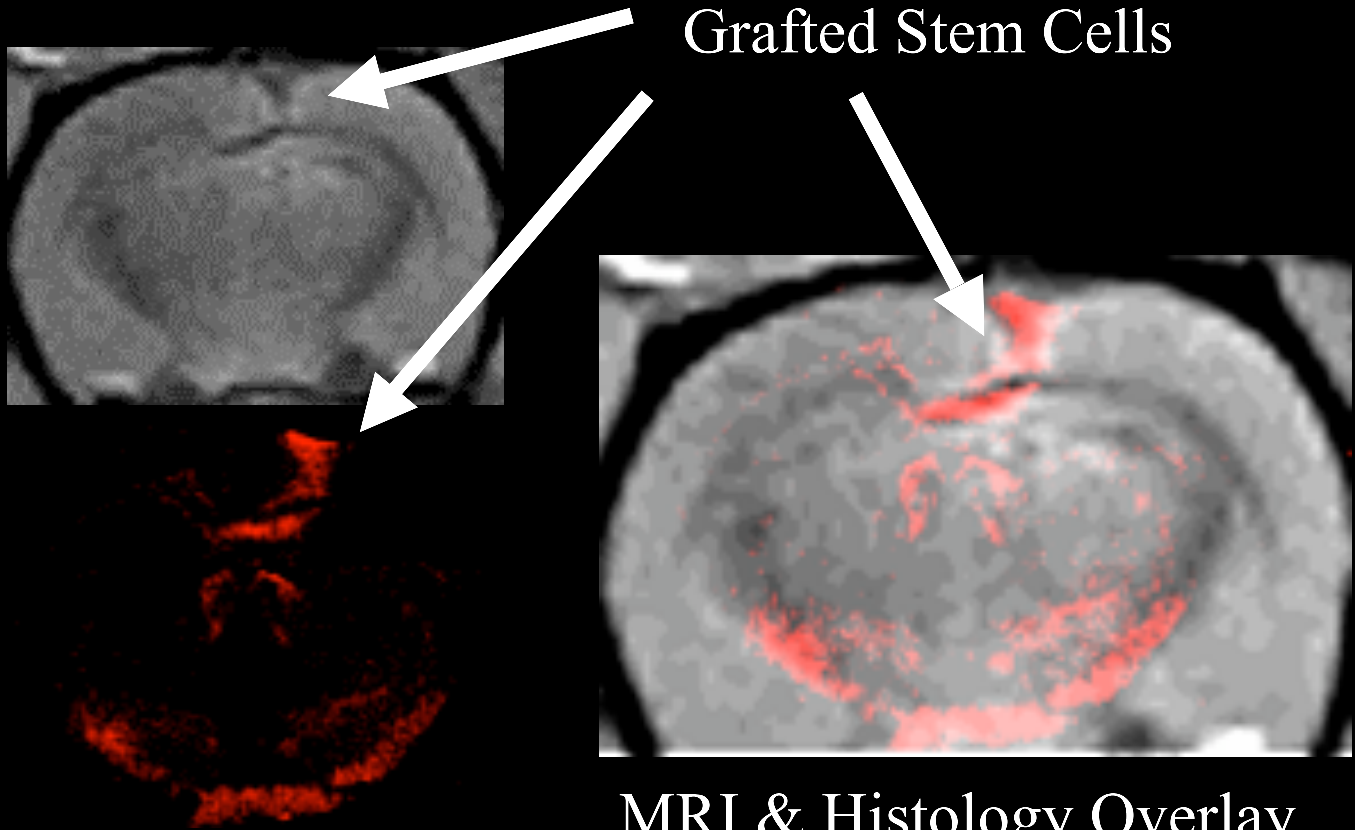




Overlay of bimodal agent

MRI

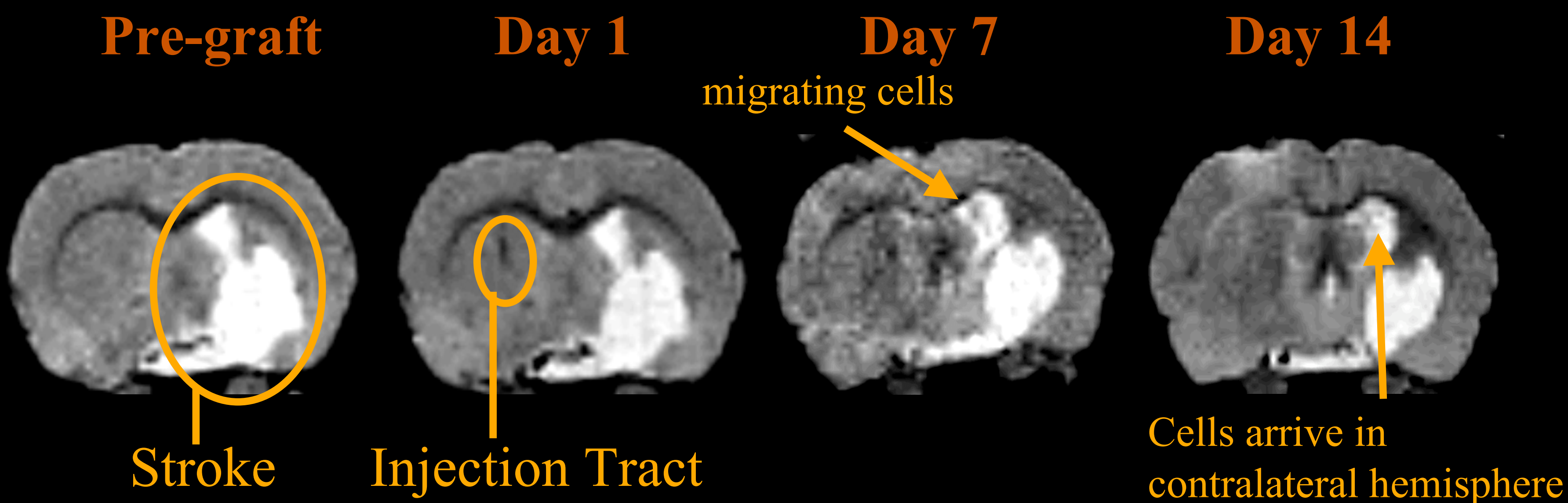
Histology



MRI & Histology Overlay

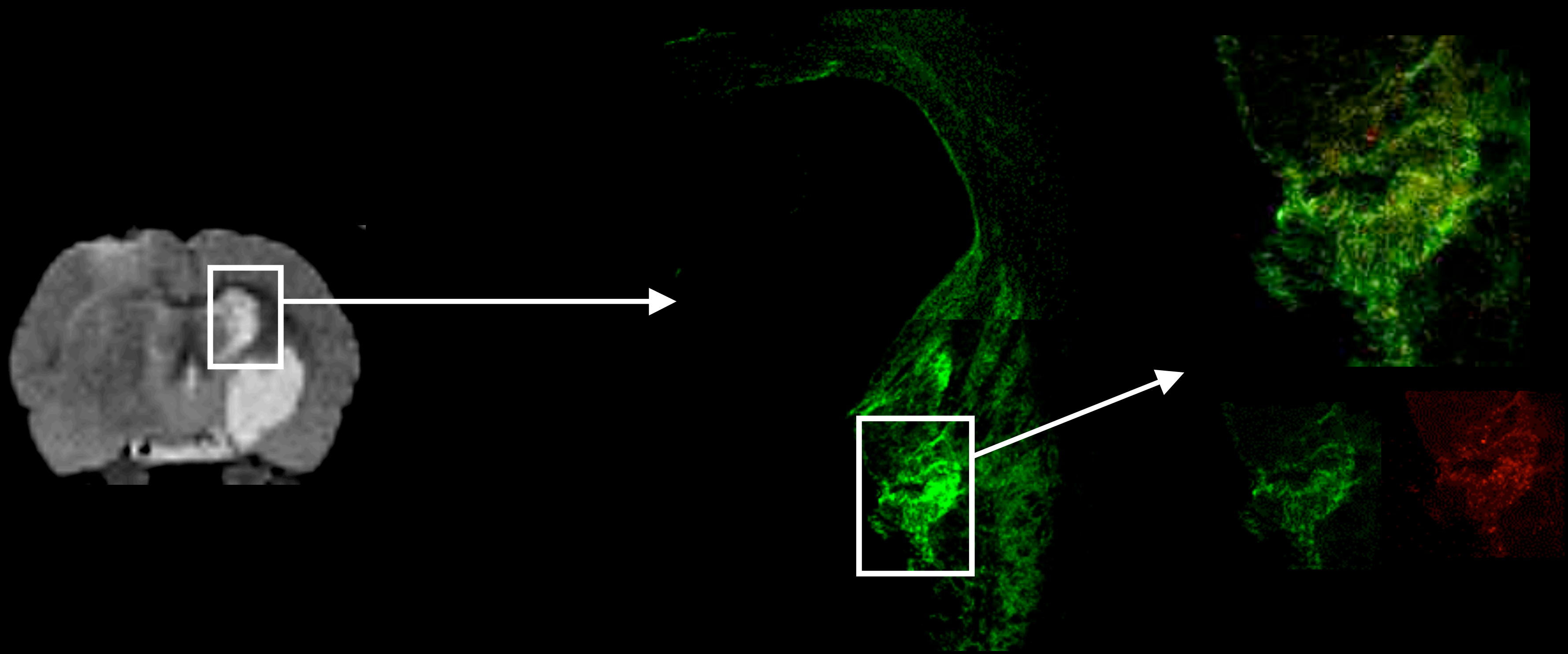
Modo et al. (2002) Neuroimage

Neuro$^{de}_{re}$generation

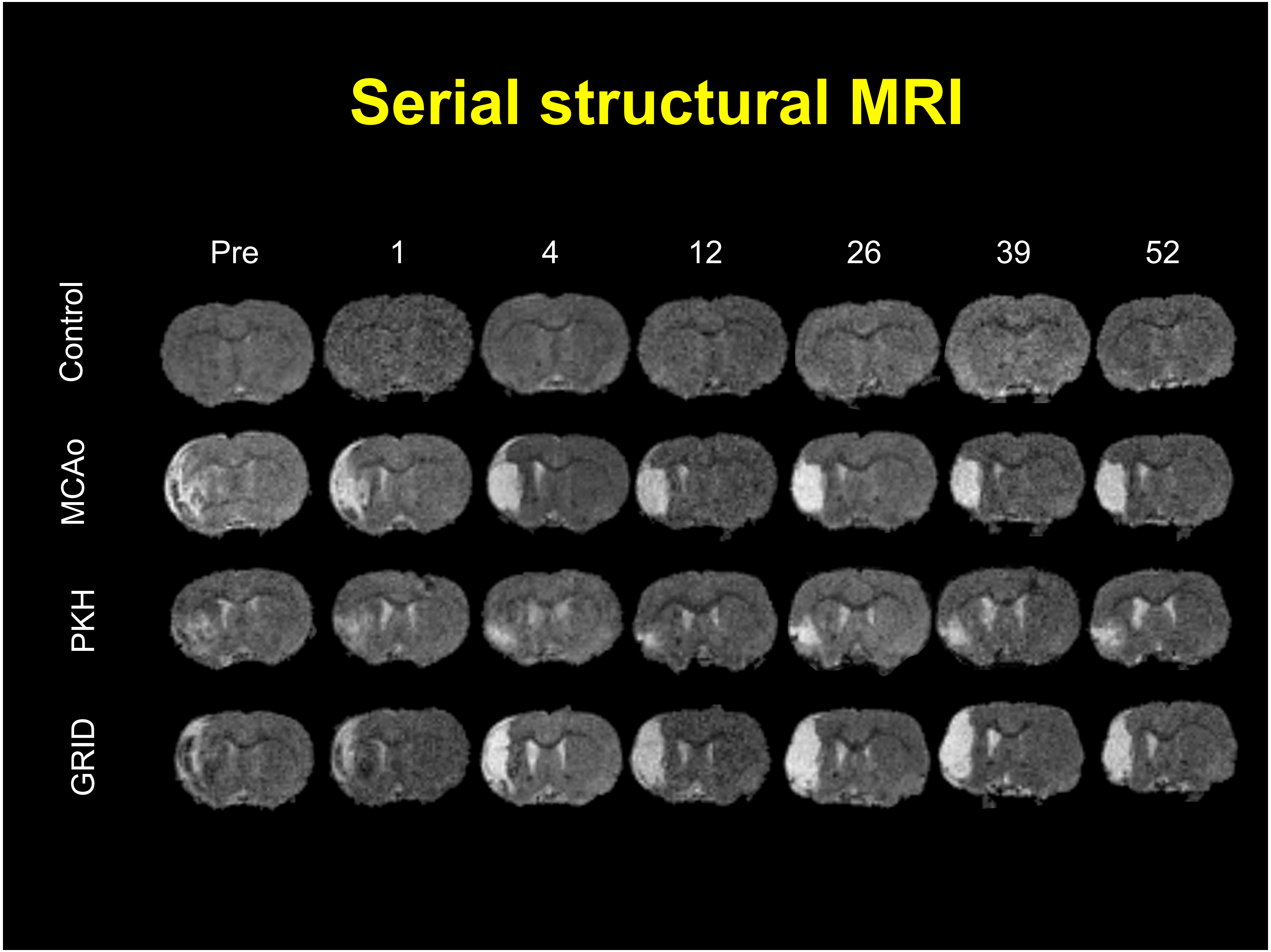


Modo et al (2004) Neuroimage

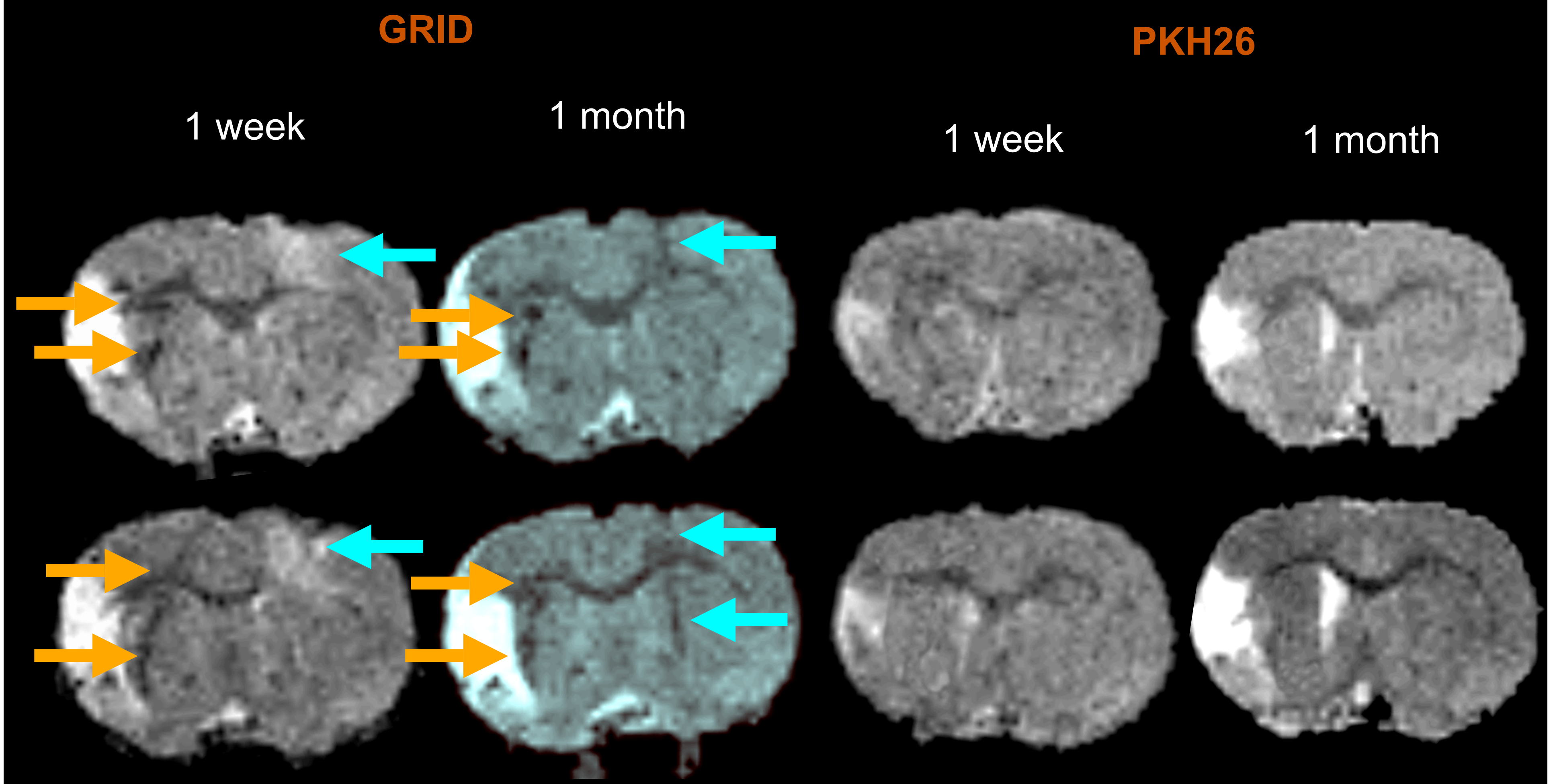
Histological detection of grafted cells



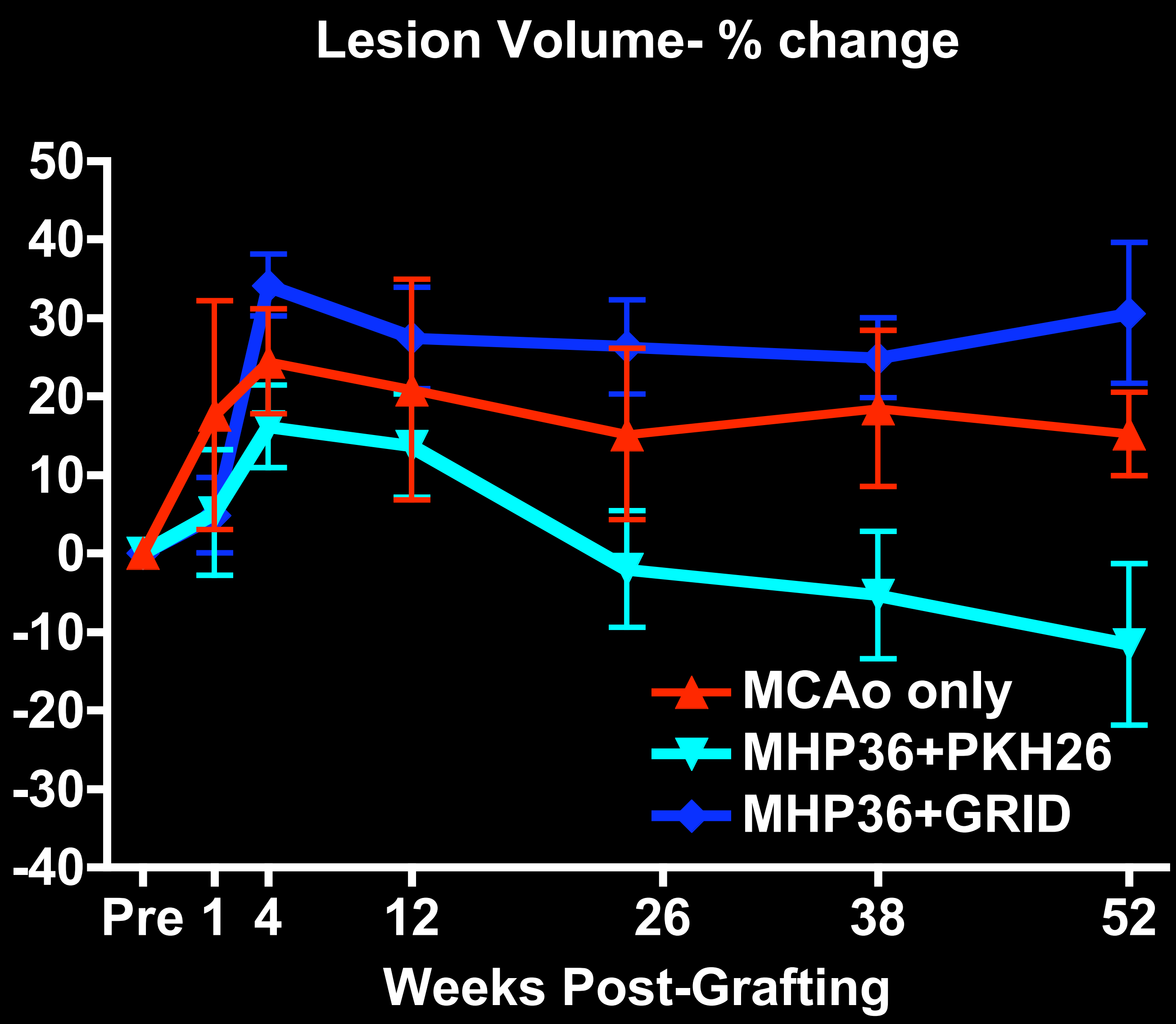
How long can we track cells in vivo?


Serial structural MRI
Pre
1
4
12
26
39
52
Control
MCAo
PKH
GRID

GRID and PKH26 compared over the first month

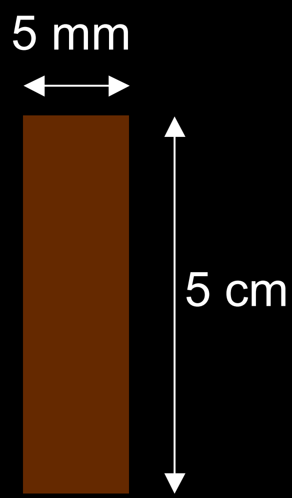


Evolution of Ischaemic Brain

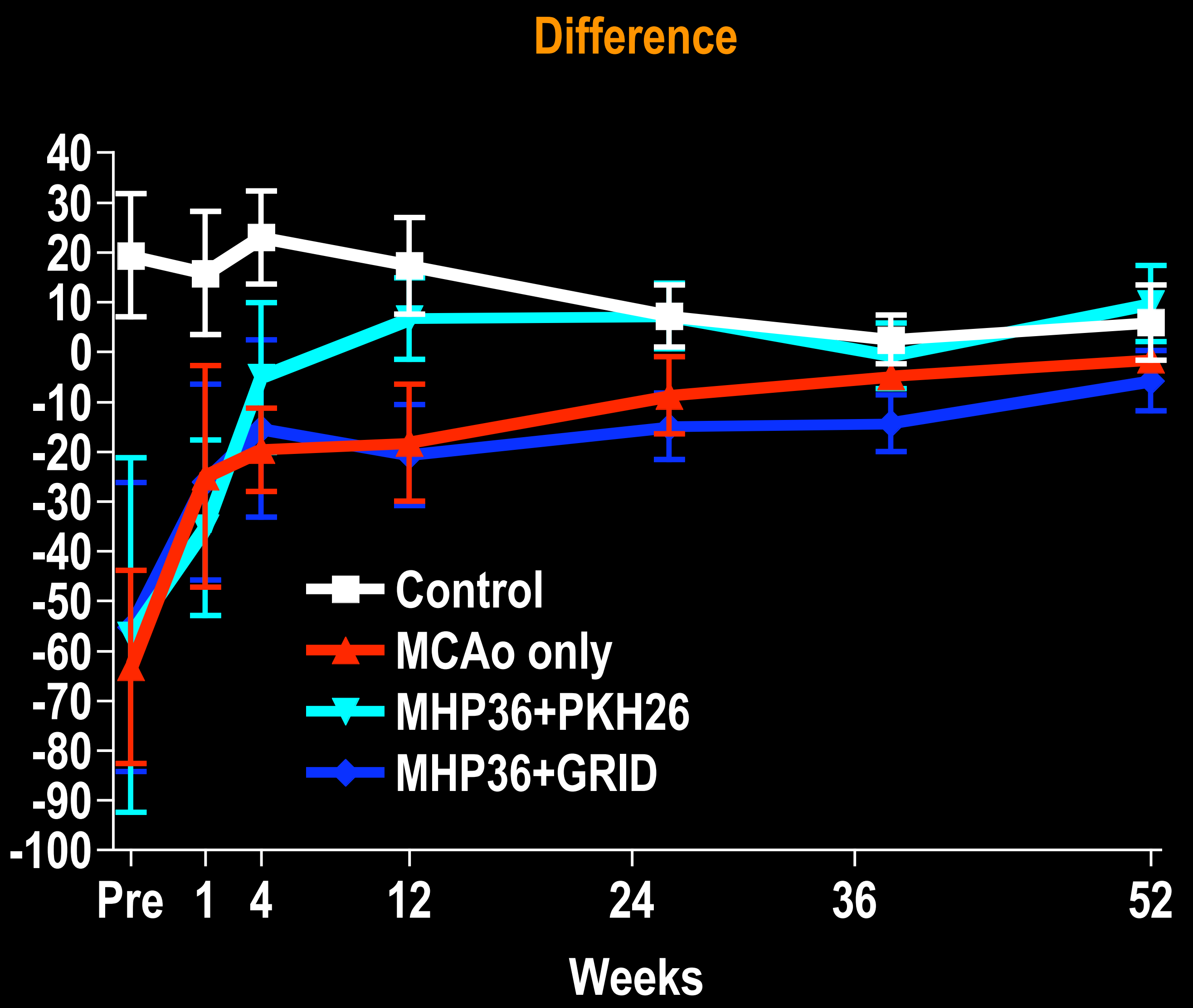


Bilateral Asymmetry Test

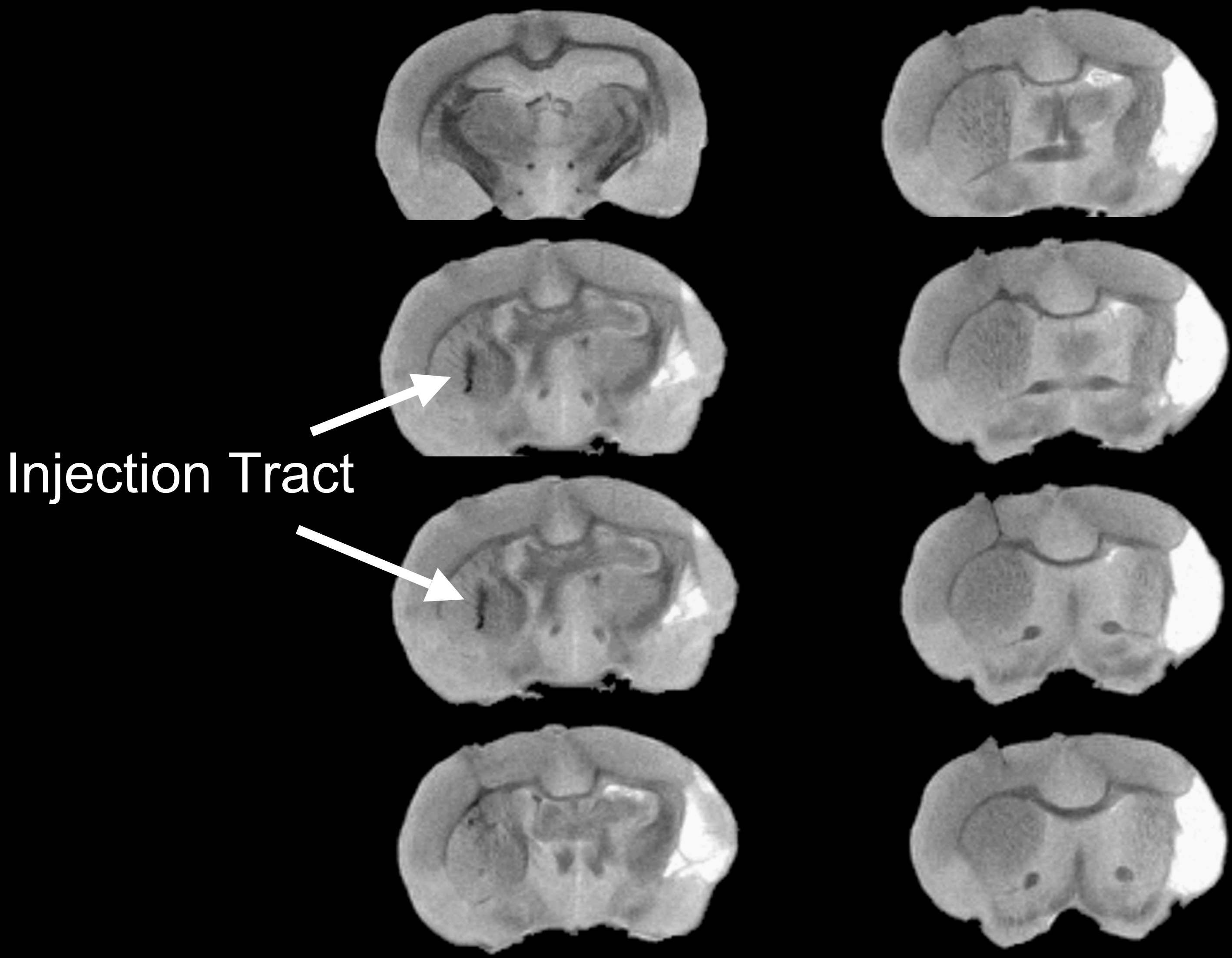
- Assessment of sensory and motor functions
- Sensitive to SMC and MC, and striatal damage
- Affected by MCAo damage
- Similar to tactile extinction test used in human patients with stroke damage



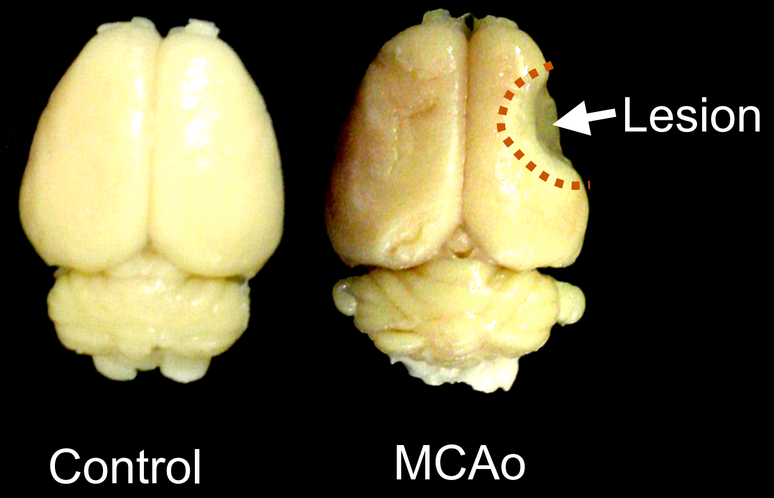
Bilateral Asymmetry Test

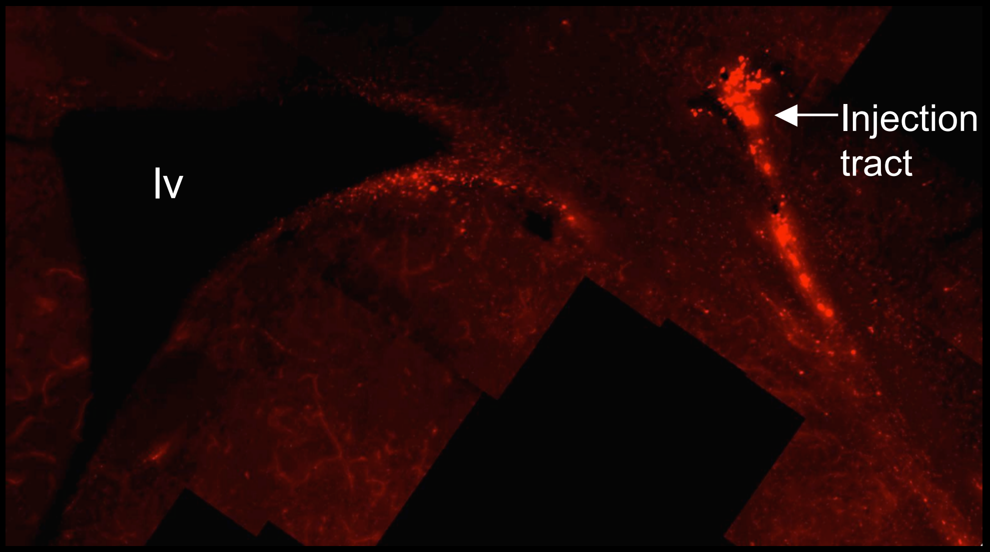


Ex vivo MR Microscopy

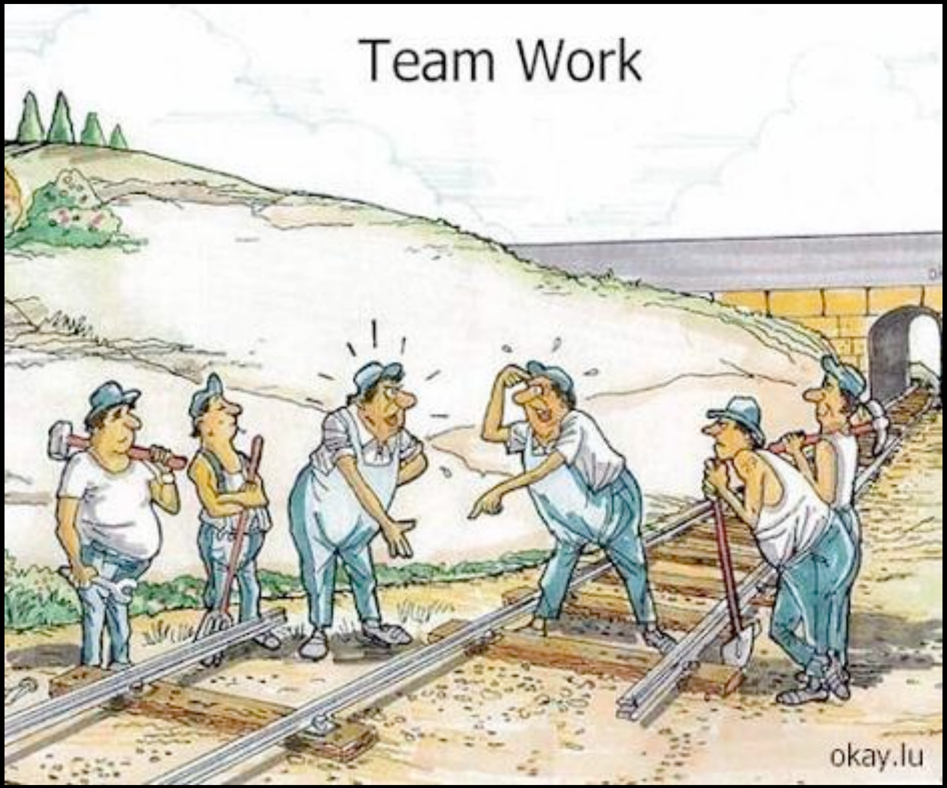


Post-mortem analyses





Collaborators



Institute of Psychiatry
Saga Johansson
Ellen Bible
Natalia Gorenkova
Anthony Vernon
Maria Ashioti
Steve Williams
Jack Price

Northwestern University
Tom Meade

Sponsors
DTI, BBSRC, NIBIB, MRC,
Edmund J. Safra Foundation

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Magnetic Nanoparticles for CNS Cell Tracking

Small Animal Management Systems
for
Multiplatform Imaging

IBMISPS

Scientific session 5: Cellular Imaging and NanoMedicine

September 6, 2007, 5:10pm-5:25pm

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Stereotaxic Surgery

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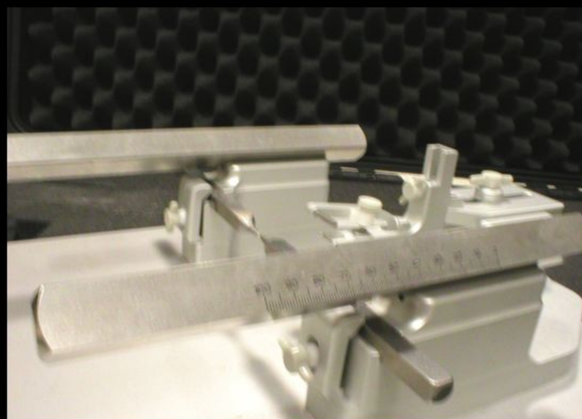

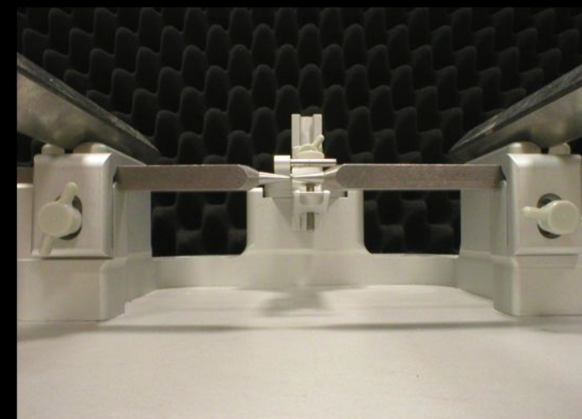

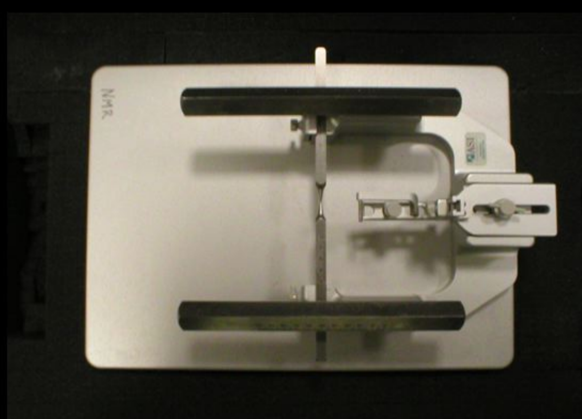

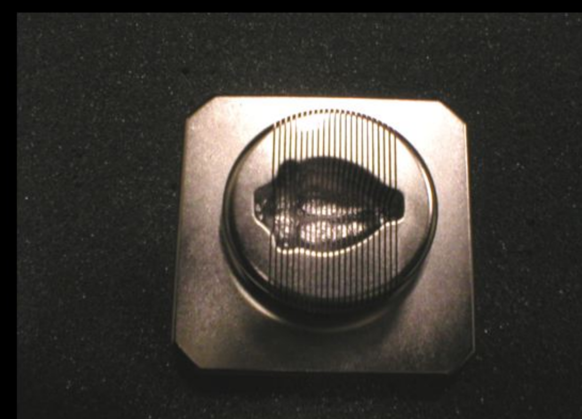

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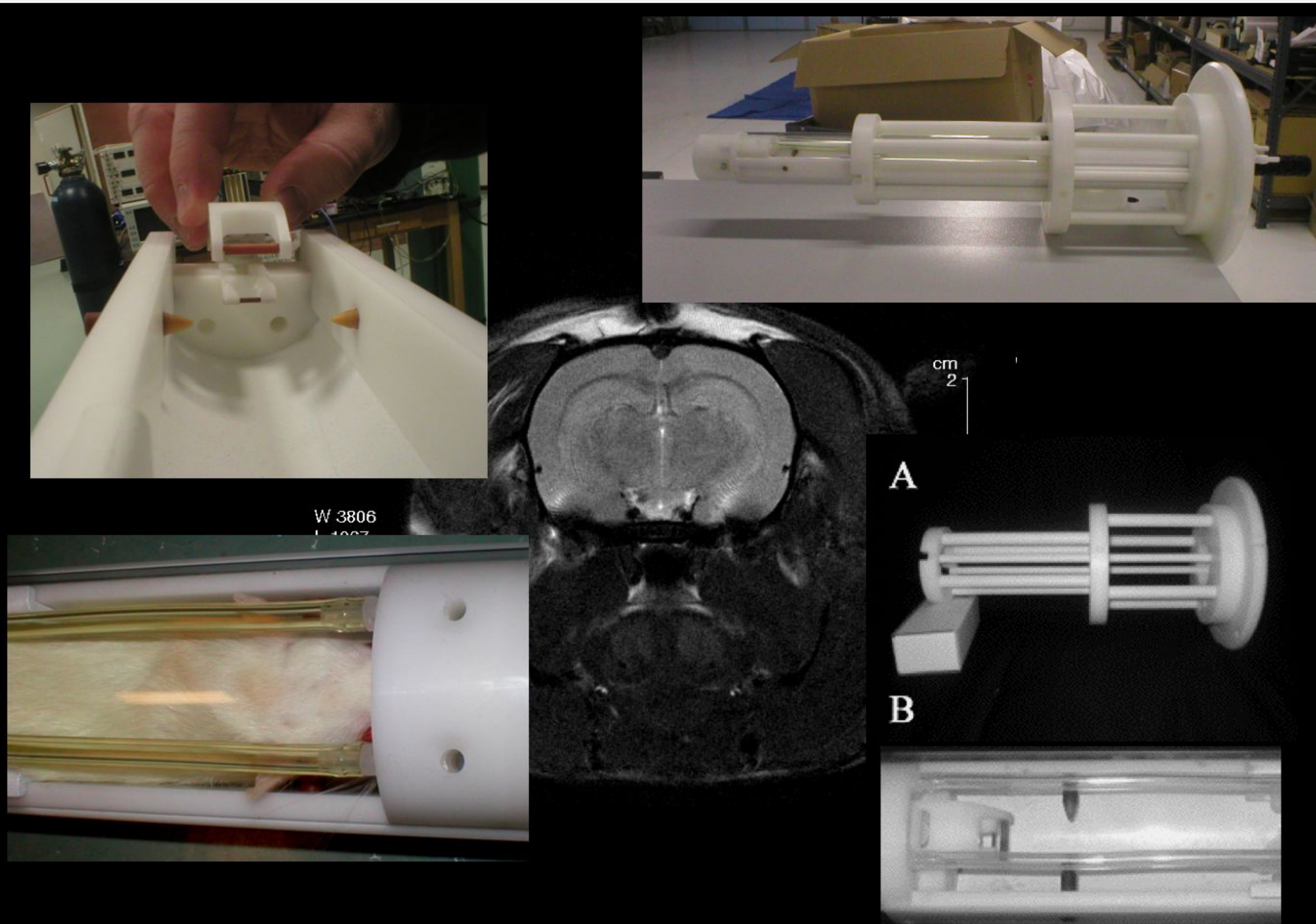
Stereotaxic Imaging



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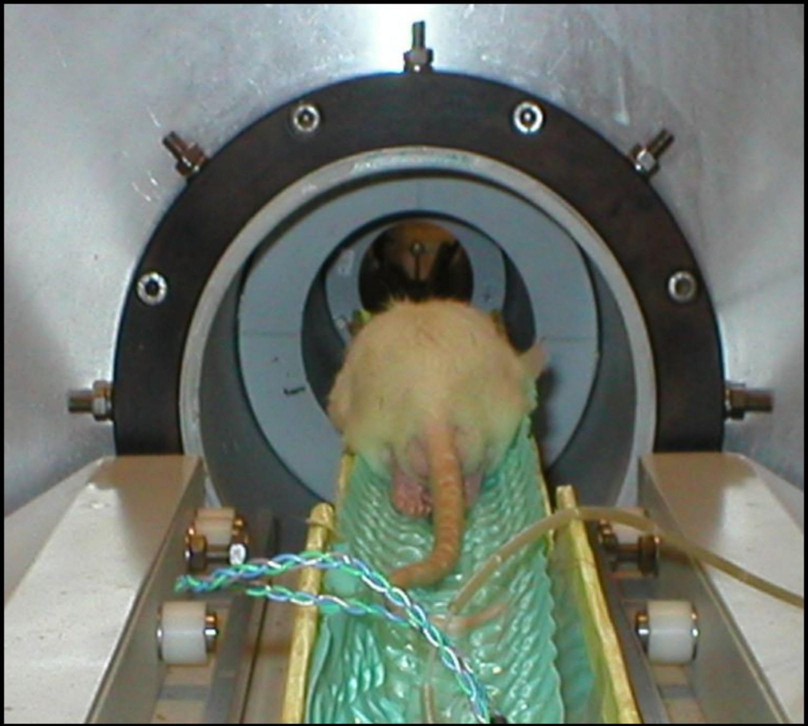
FAC



- Most humans are all animal
- Not all animals are human
- You have a head on your shoulders…

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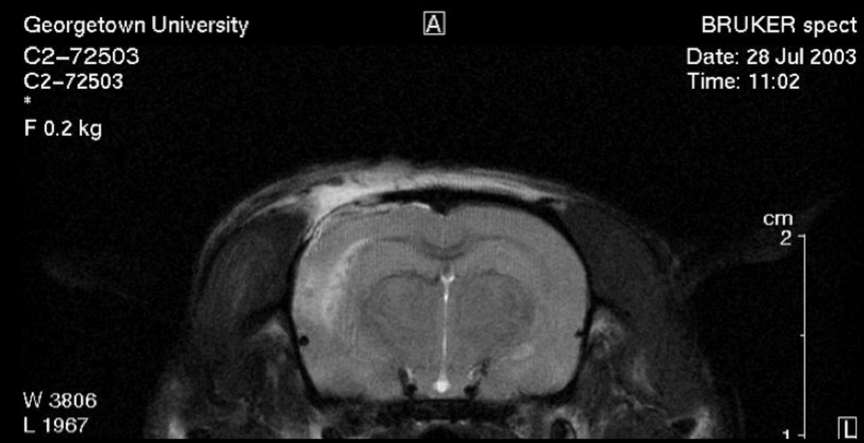
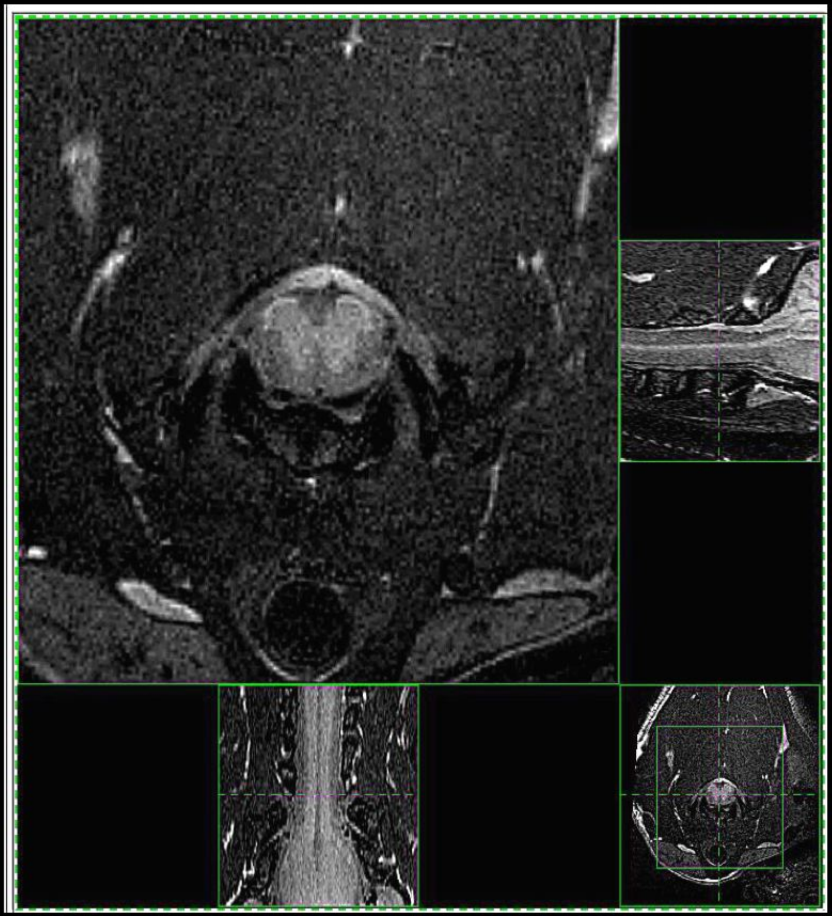
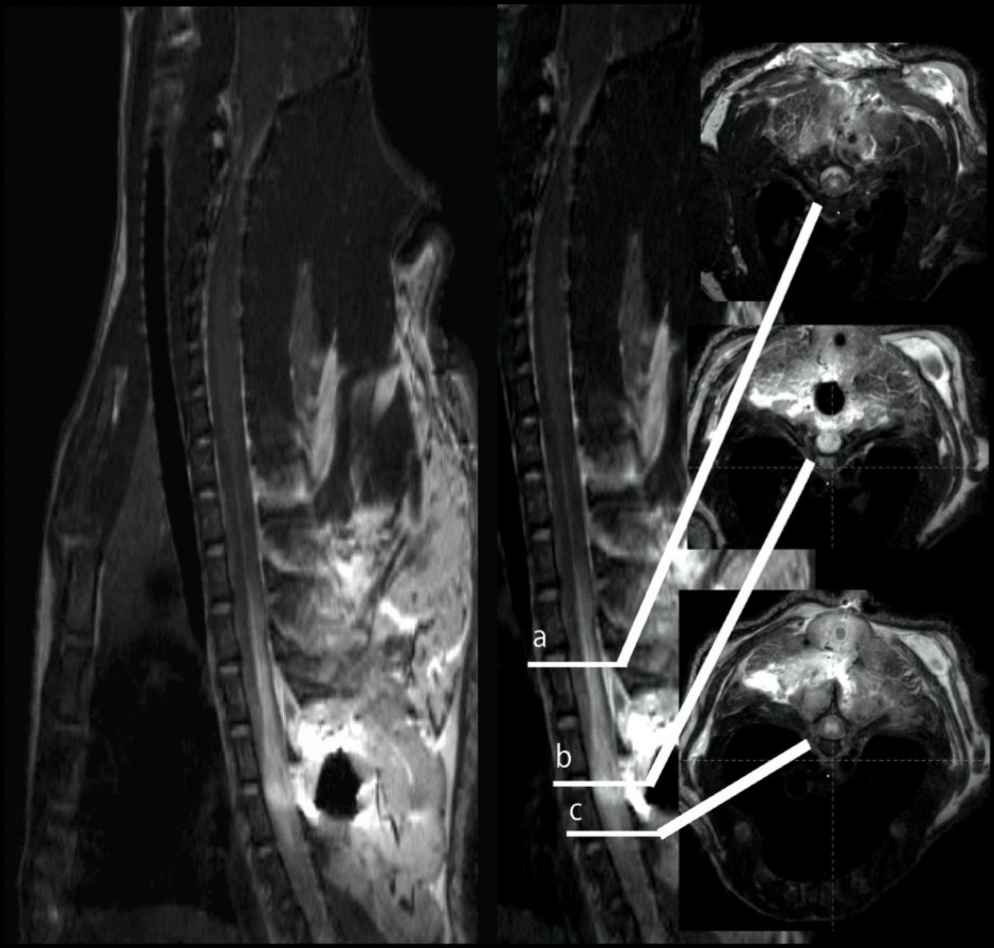
MRI Histology



Novel Contrast Agents





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Contrast: In-Vivo, In-Vitro

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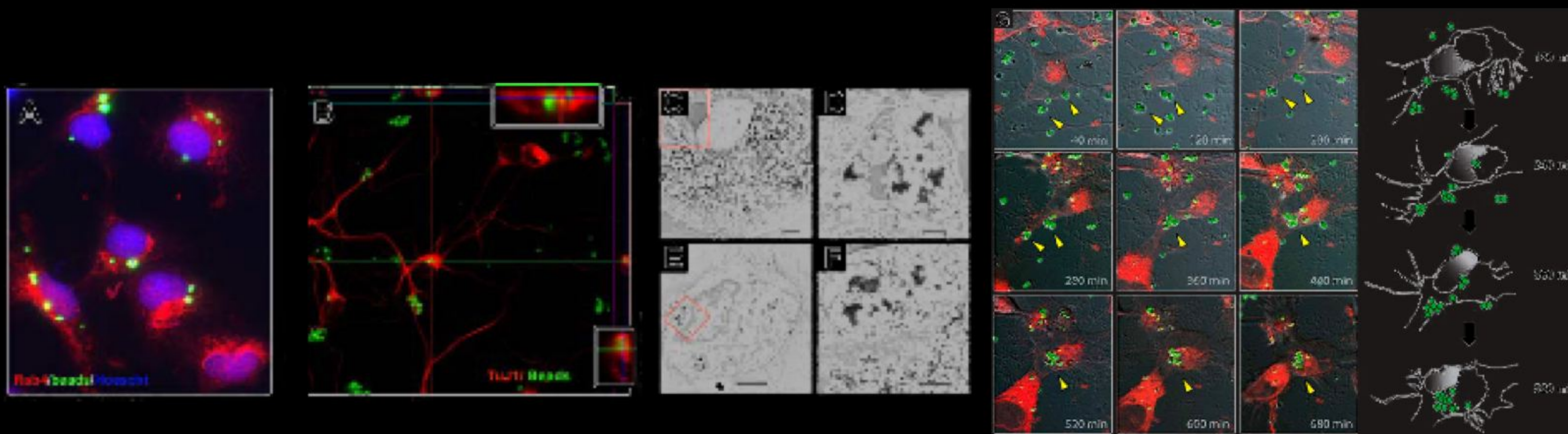

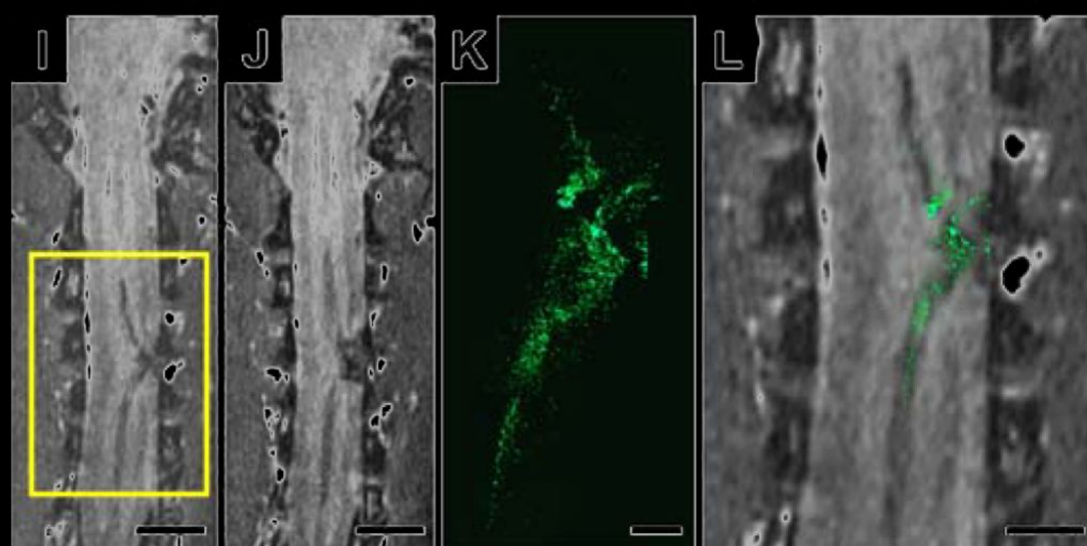

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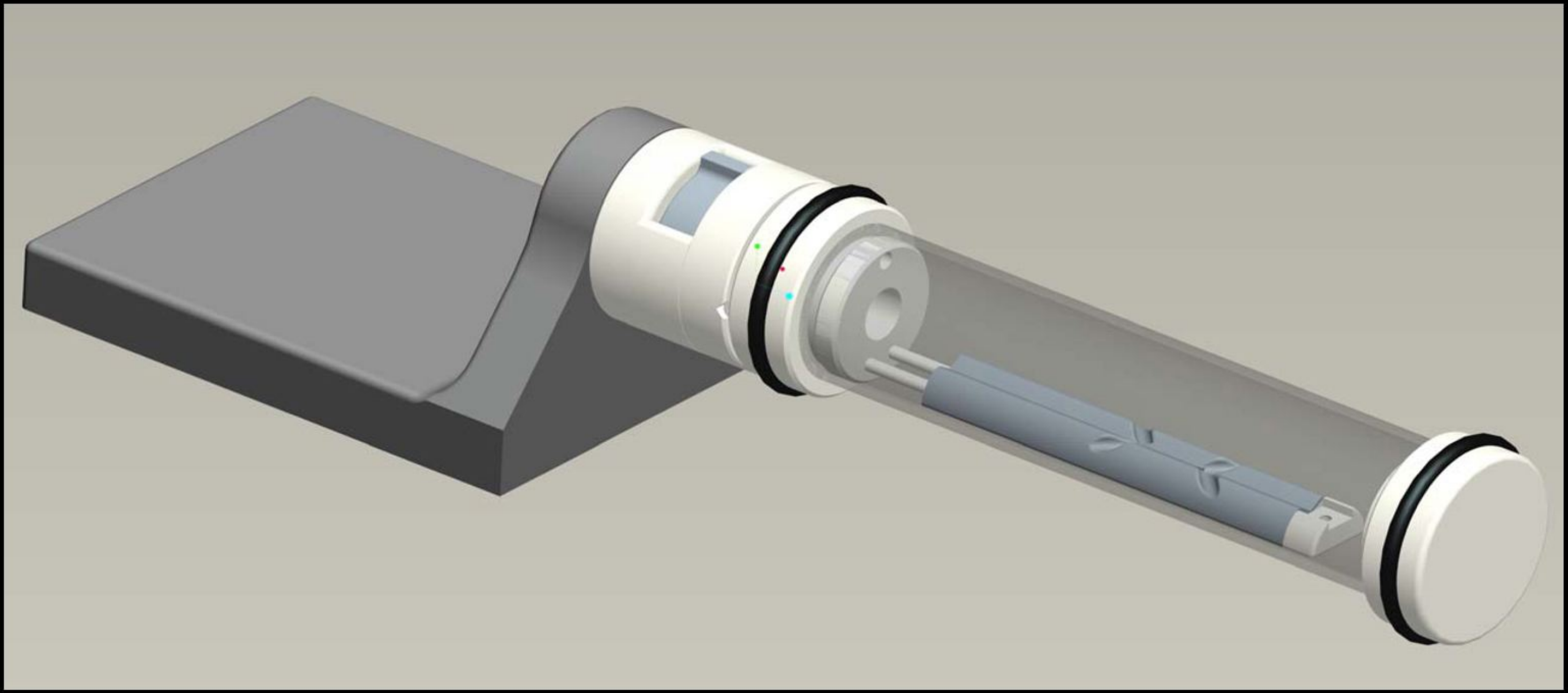
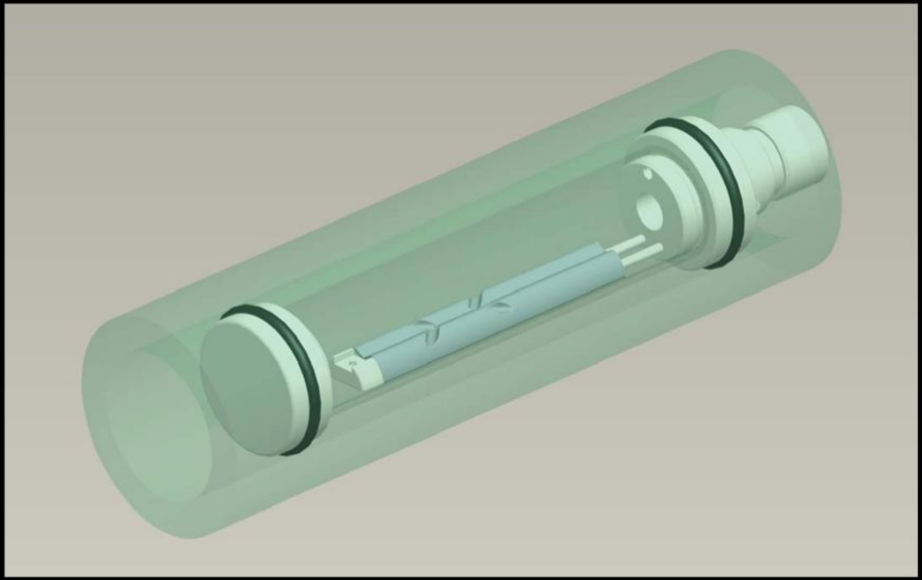
Future Directions



Isolation

- Concept not patented by GUMC.

- New Design in Transport conduit.



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Concept of Integrated Imaging

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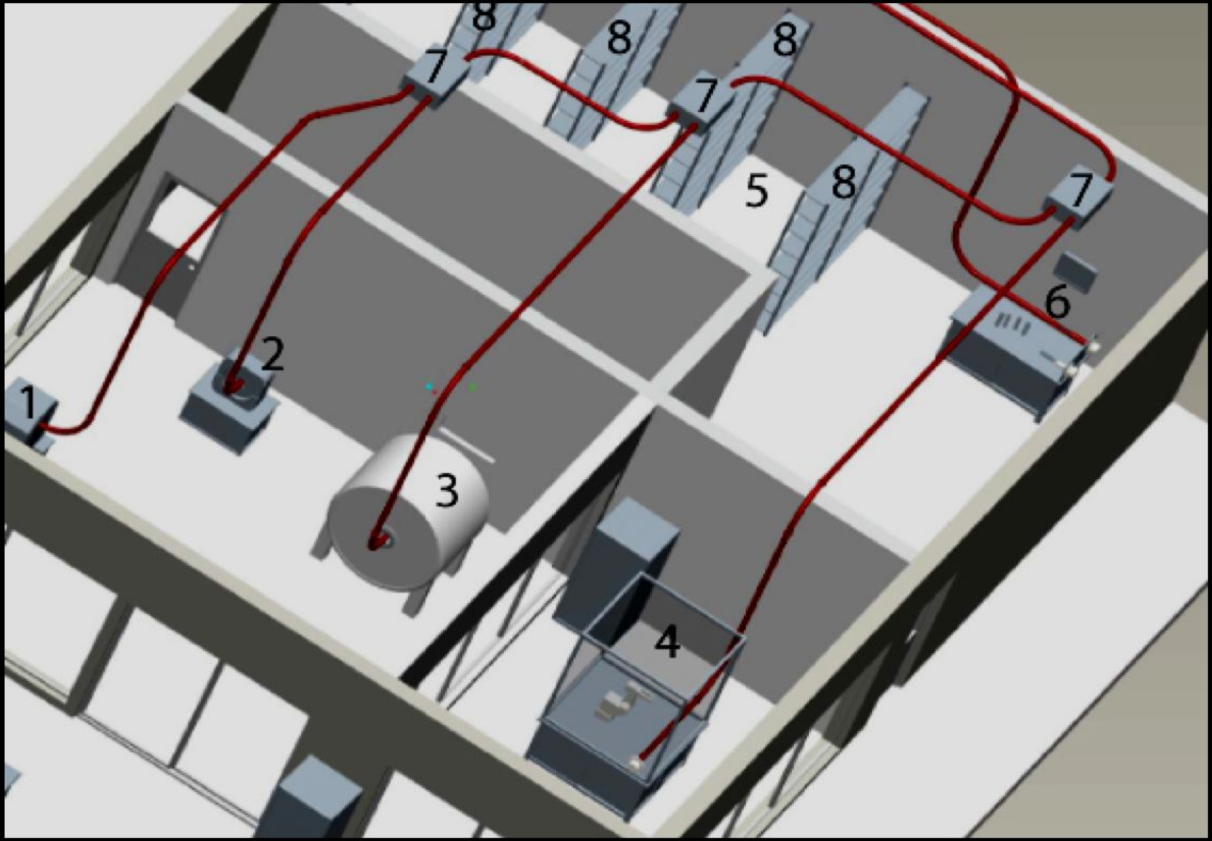

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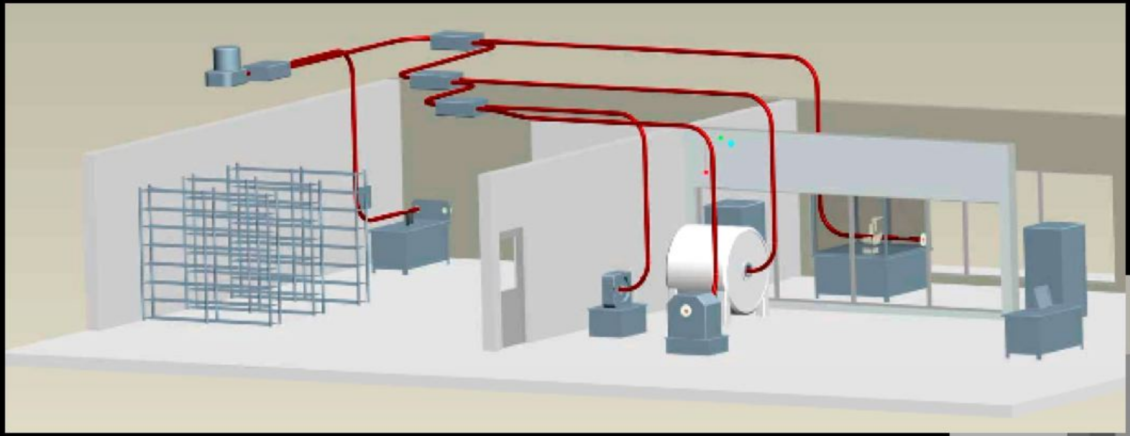
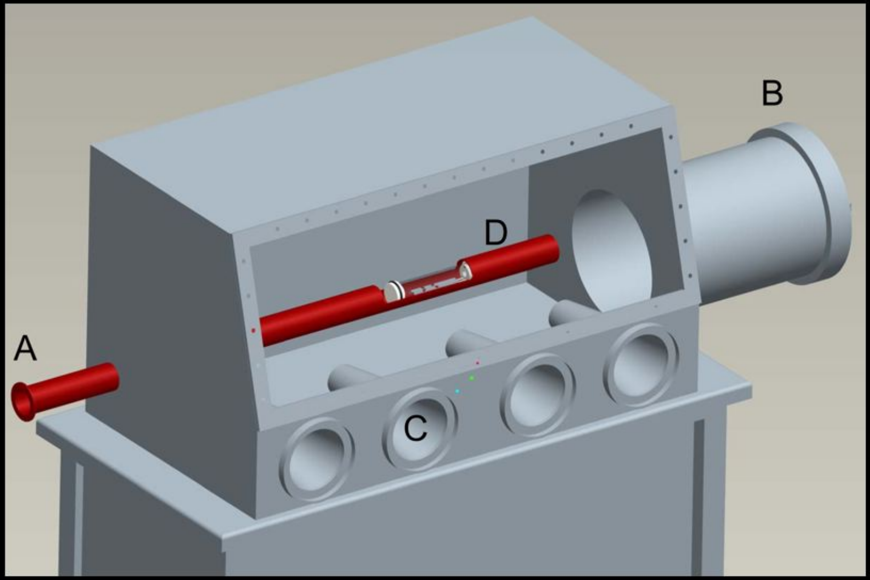
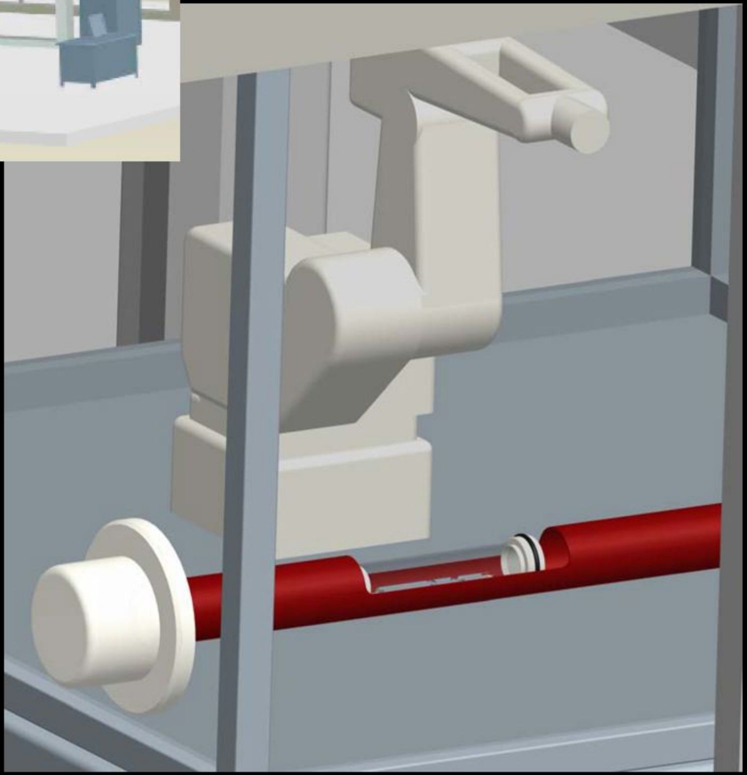
Concept of Integrated Imaging







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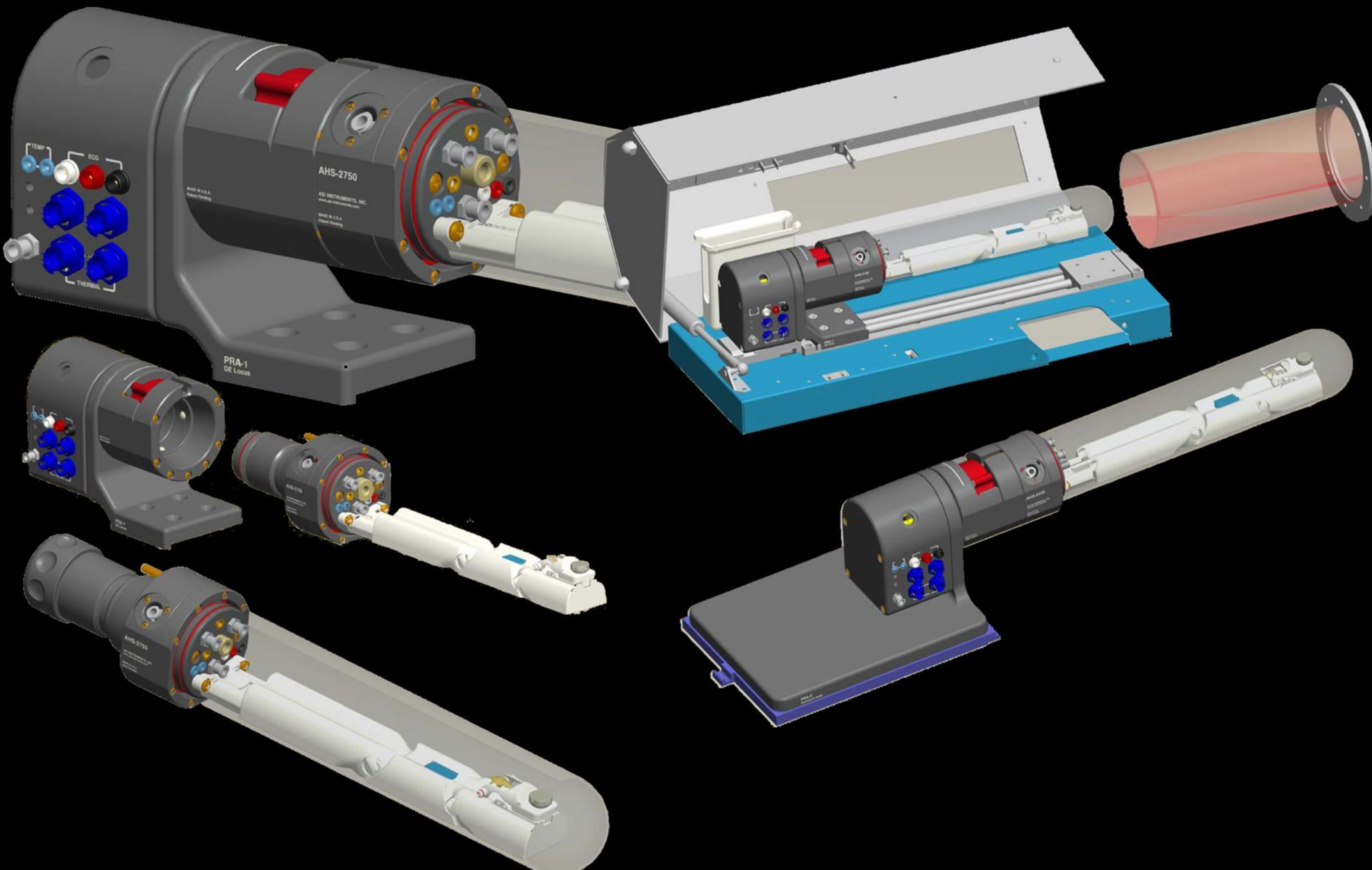
Animal Management

Children's National Medical Center®



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Prototype Implementations

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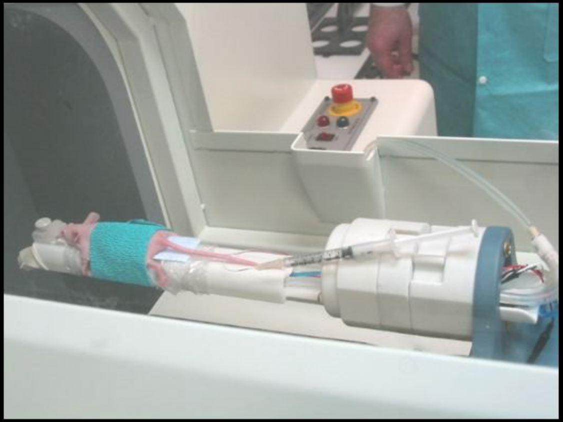

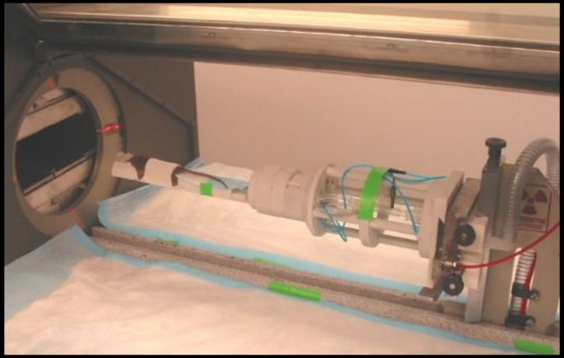

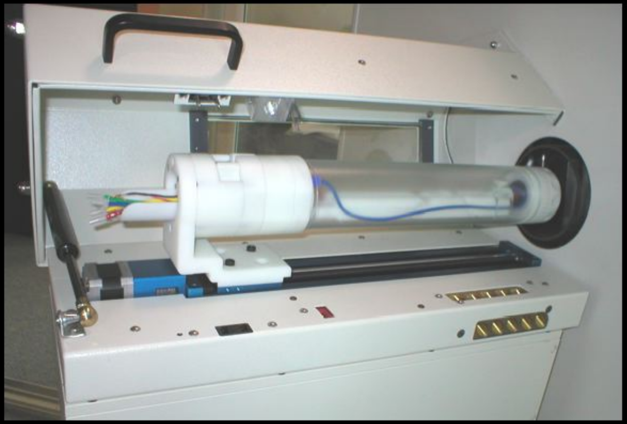

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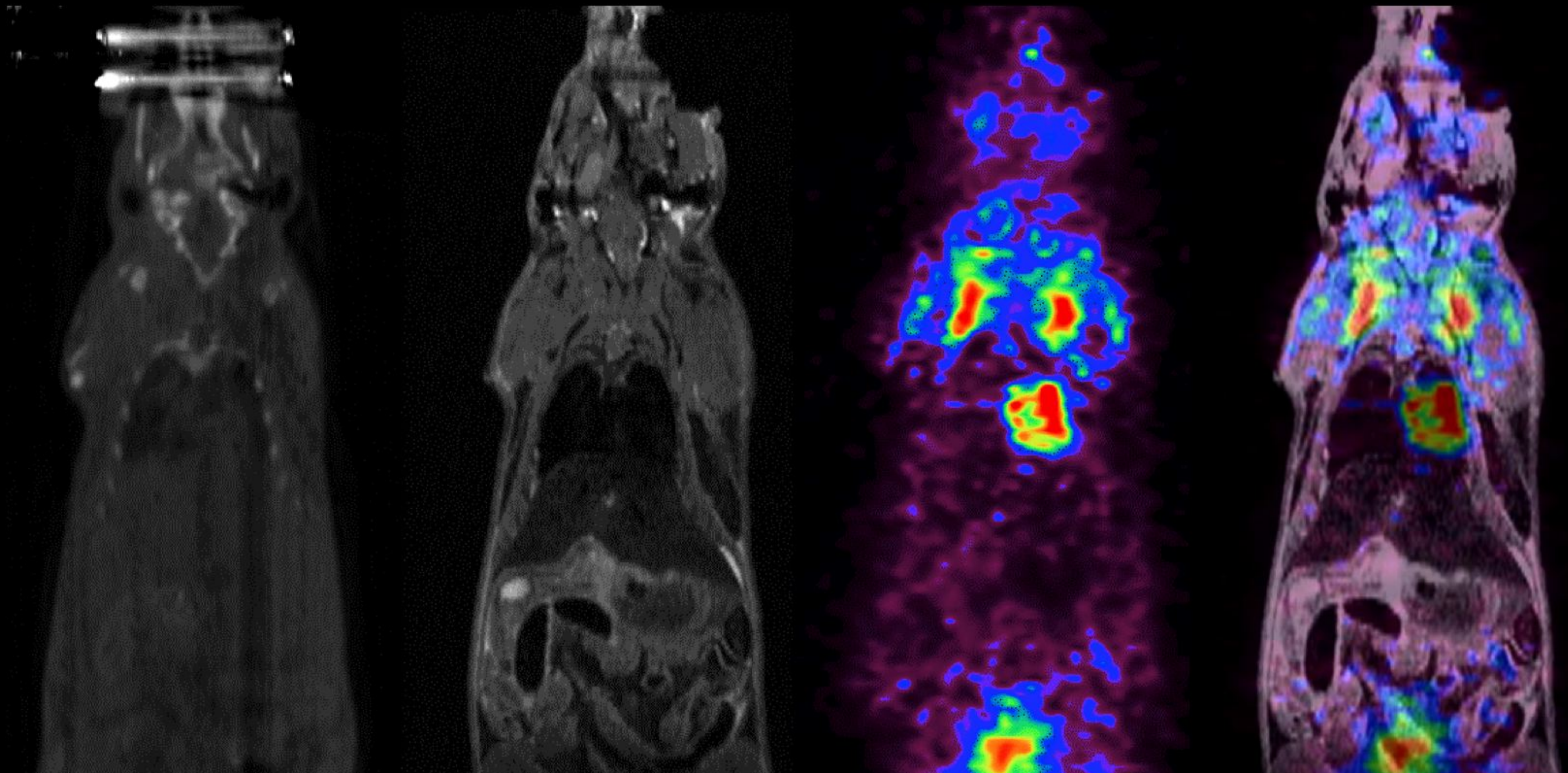
Day 1 – MR/PET/CT, Viral Agent

CT MR PET MR-PET



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Multimodality Imaging

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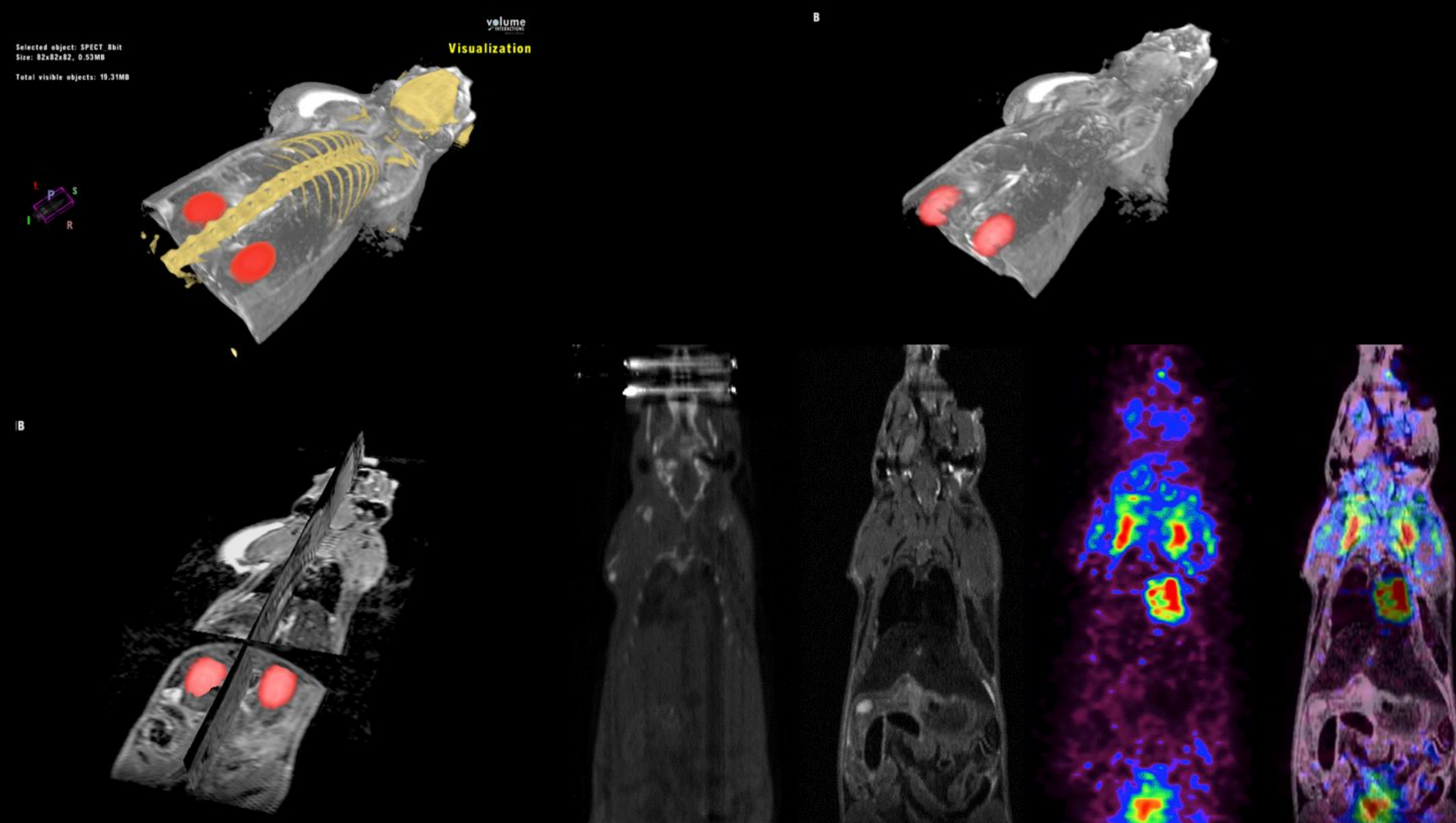
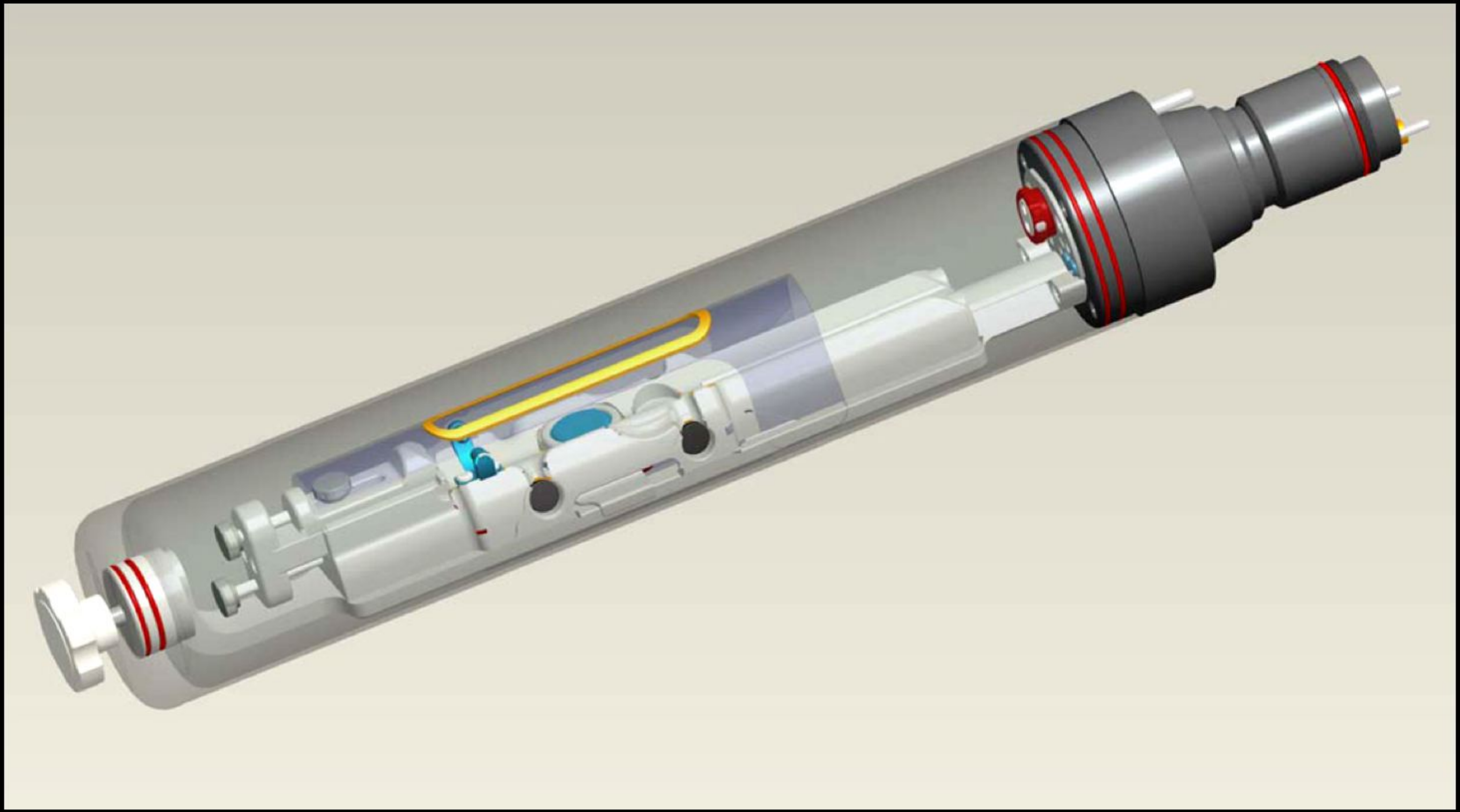


More Detail on Design



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Realization

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Leica CM3600 Cryomacrotome

For larger samples such as a rabbit or monkey, a special version of the instrument with a manually height-adjustable knife holder for speci- mens up to 200 mm high is available on request. be printed. A password and user identification are required to open and close the system. The system administrator ensures that only approved users have access to various levels within the operating

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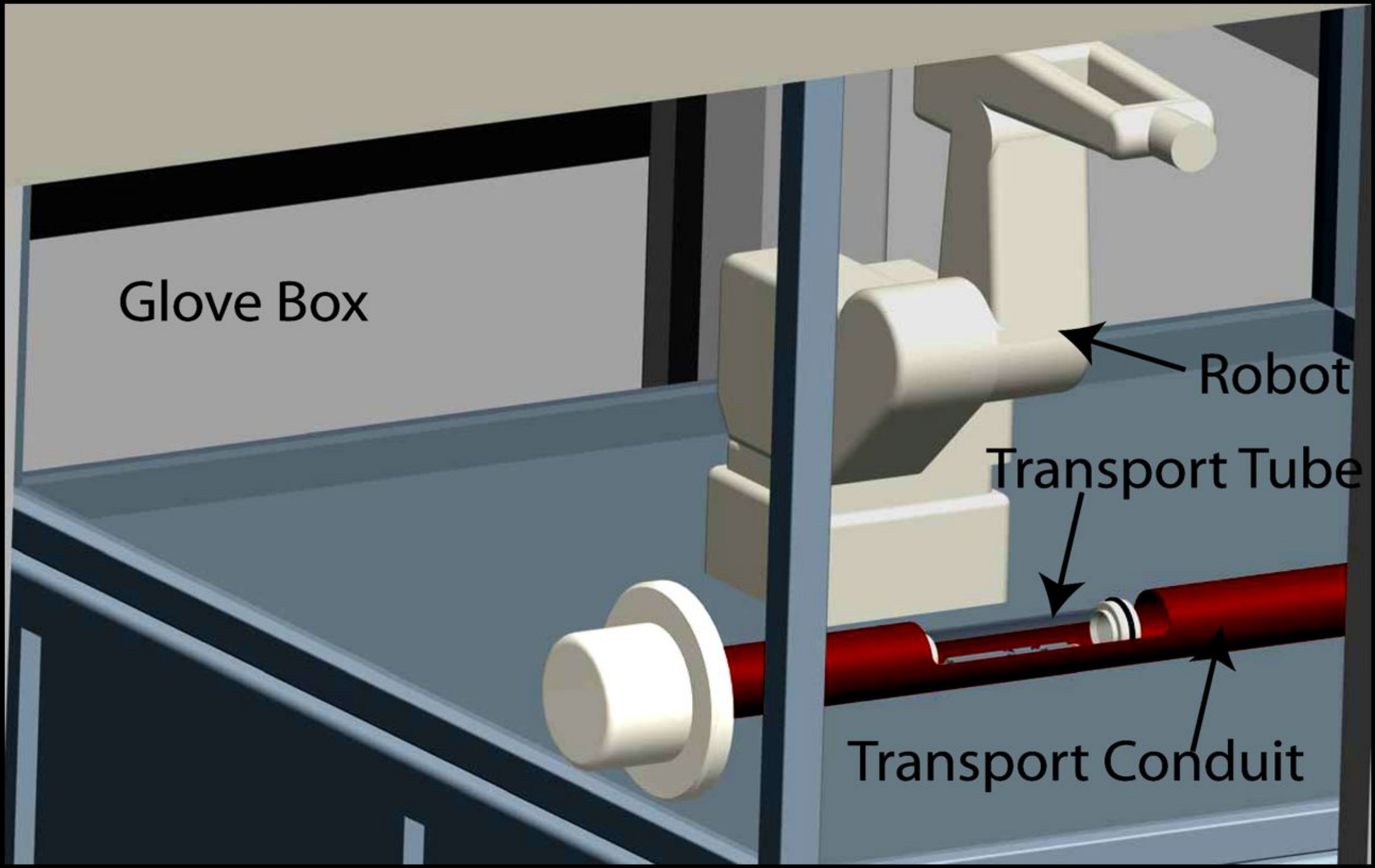
Glove Box



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Reverse Engineering Anatomy

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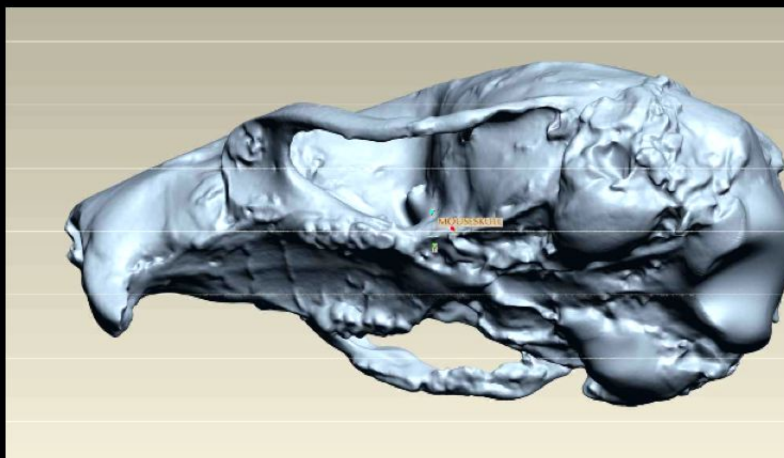

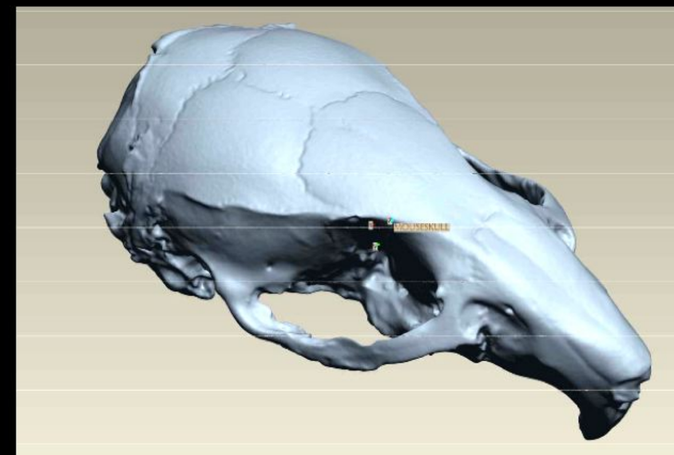

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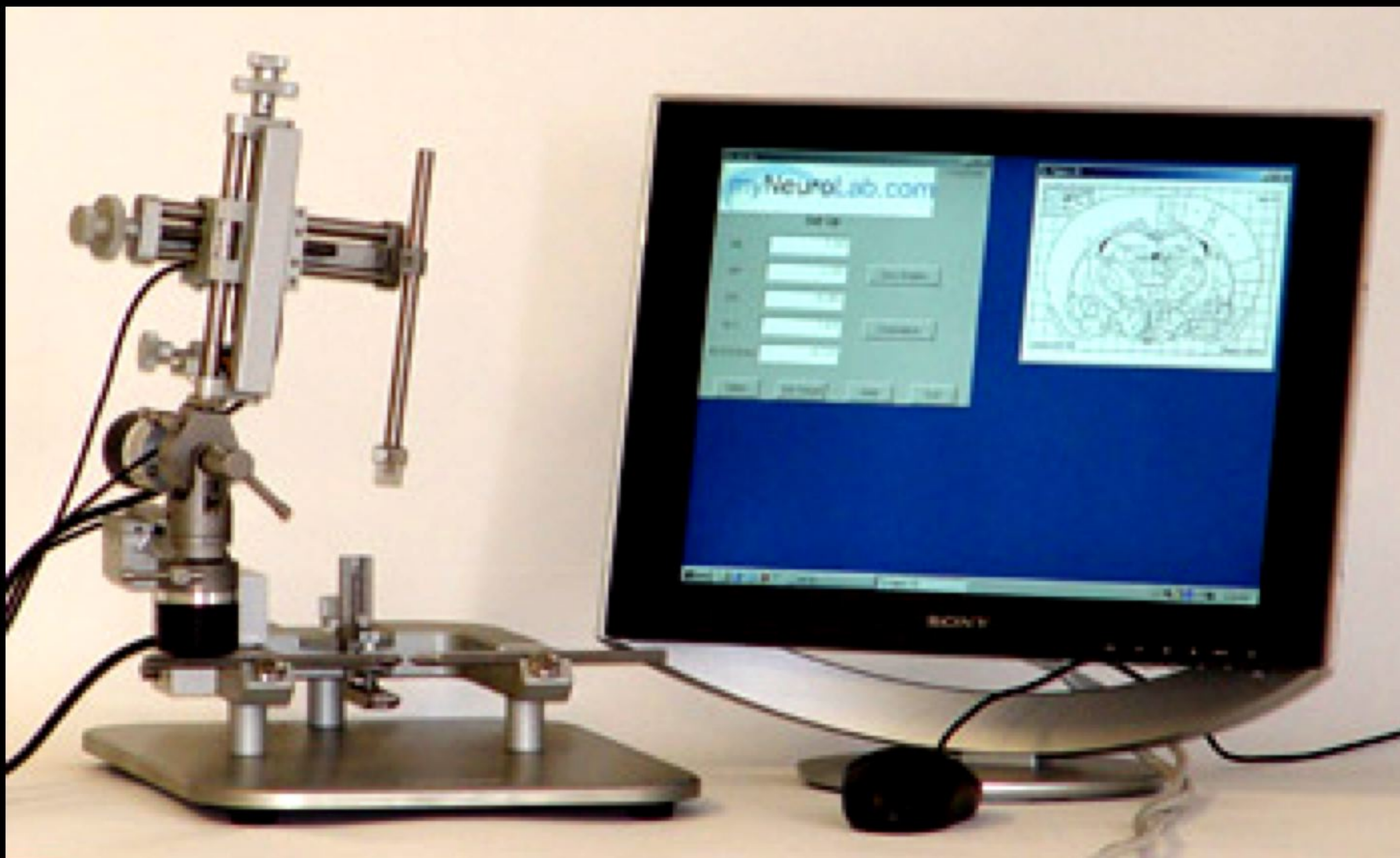
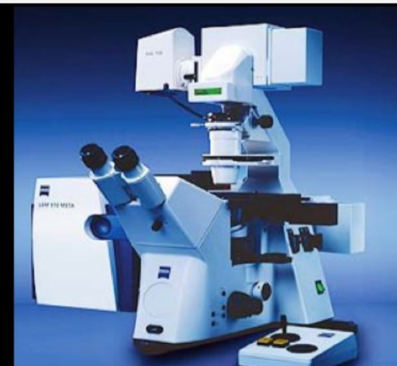
Today's Products

Children's National Medical Center

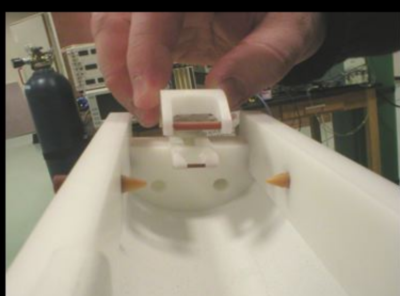


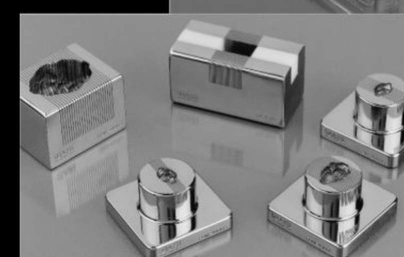
GEORGETOWN UNIVERSITY MEDICAL CENTER

Today’s Products



Original NIH IR Laser LCM (Science 278:998-1001,1996)





GEORGETOWN UNIVERSITY MEDICAL CENTER

Children's National Medical Center®

Histological Sectioning

GEORGETOWN UNIVERSITY MEDICAL CENTER

THANK YOU!

Children's National Medical Center®

Small Animal Management Systems

for

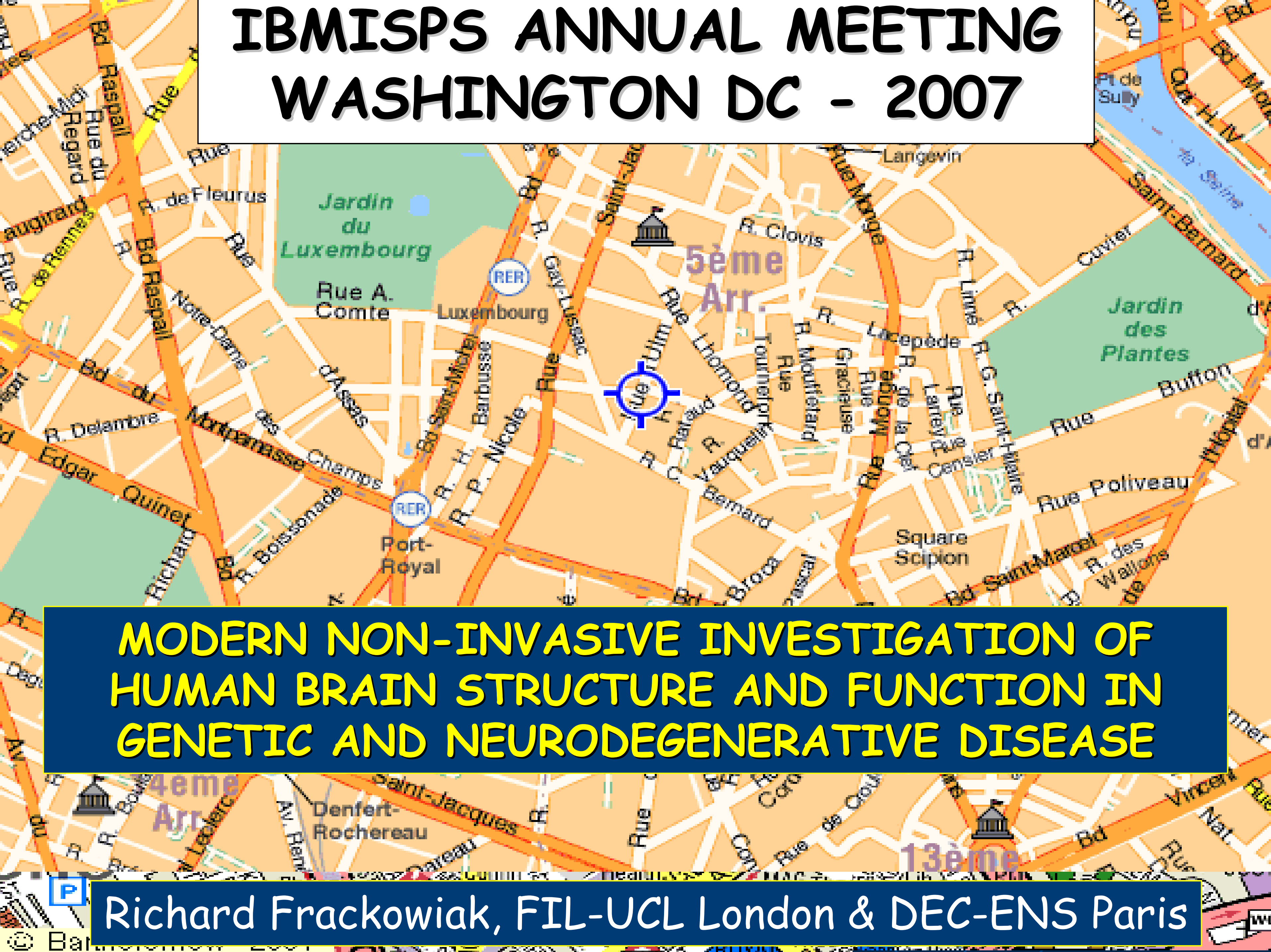
Multiplatform Imaging and … histology?

IBMISPS

Scientific session 5: Cellular Imaging and NanoMedicine

SEPTEMBER 6, 2007, 5:10pm-5:25pm

IBMISPS ANNUAL MEETING WASHINGTON DC - 2007



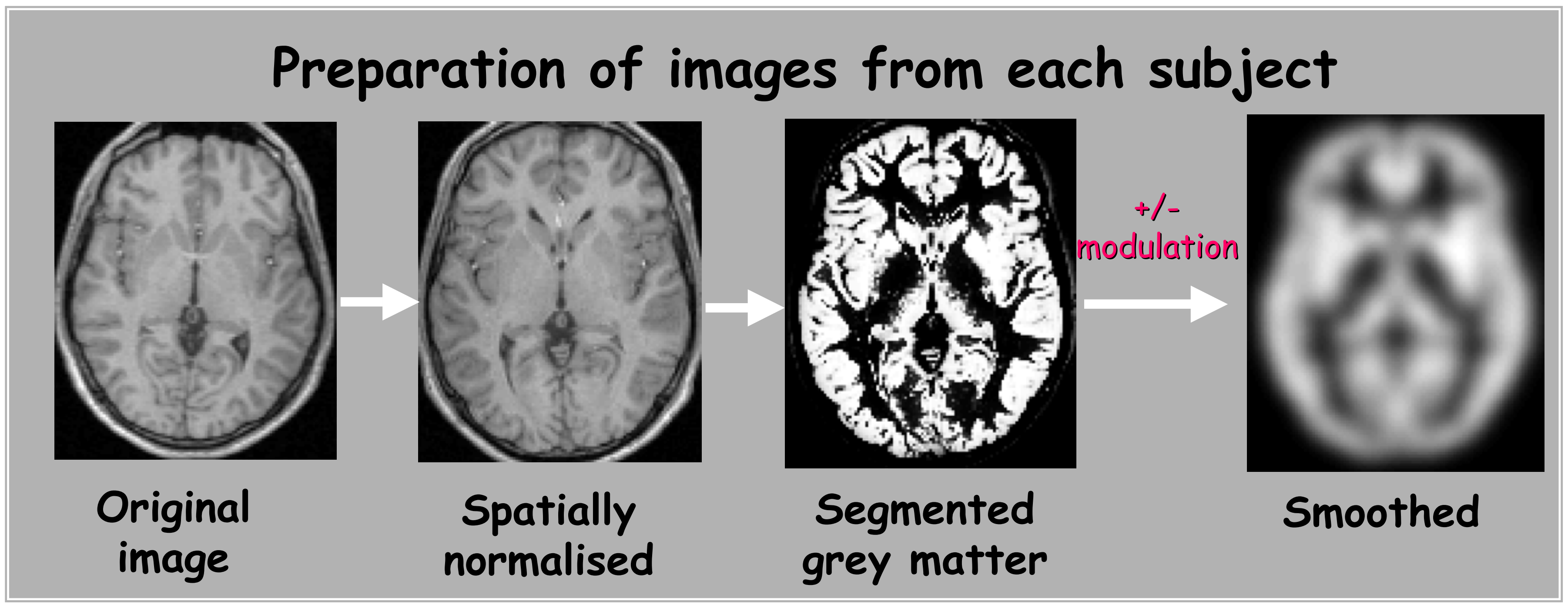
MODERN NON-INVASIVE INVESTIGATION OF HUMAN BRAIN STRUCTURE AND FUNCTION IN GENETIC AND NEURODEGENERATIVE DISEASE

Richard Frackowiak, FIL-UCL London & DEC-ENS Paris

CHARACTERISING BRAIN STRUCTURE

- Resolution
- Structural correlations
- Structural biomarkers of preclinical disease
- Structural connectivity
- Genetics and structural variability

VOXEL BASED MORPHOMETRY



A voxel by voxel statistical analysis is used to detect regional differences in the amount of grey matter between populations.

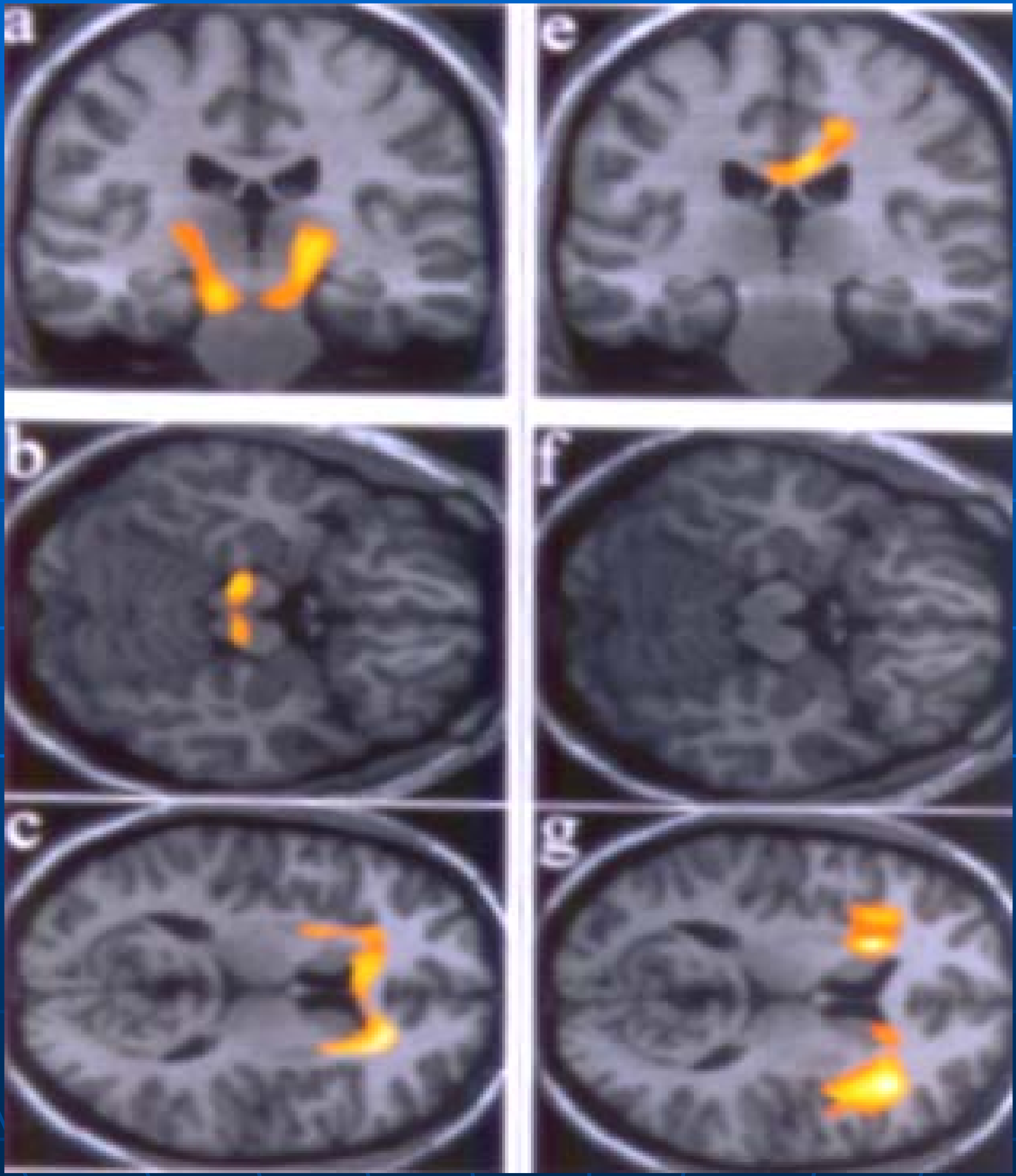
ONE MUTATION MULTIPLE PHENOTYPES

EXAMPLE:
KALLMANN'S SYNDROME

Autosomal dominant multiple facetted neuro-endocrine syndrome; 50% patients exhibit mirror movements

Pruning of uncrossed pyramidal fibres is a normal early infantile developmental feature

KALLMANN'S SYNDROME



With vs without mirror movements

Genetics and structural variability

PRE-CLINICAL BIO-MARKERS

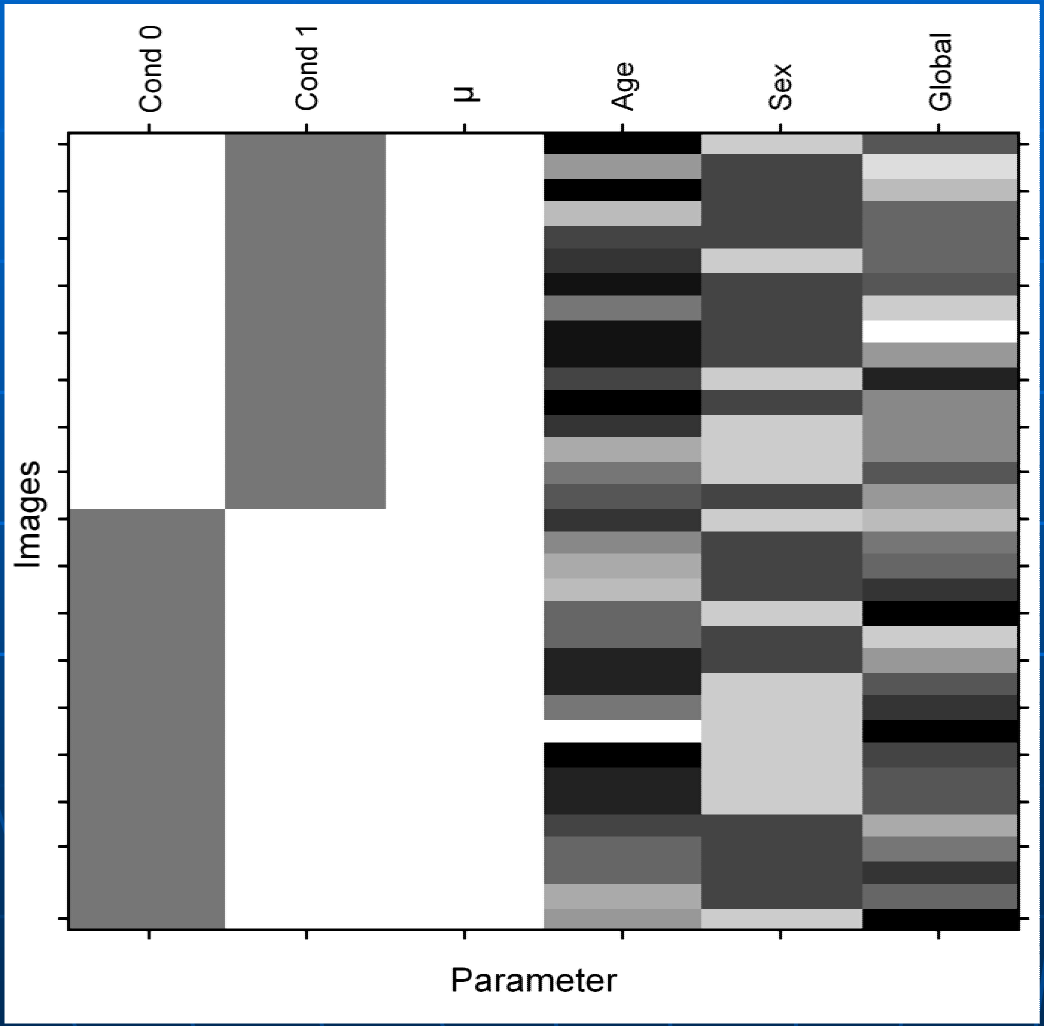
EXAMPLE:

HUNTINGTON'S DISEASE

Model disease with gold standard reference provided by quantitative nature of huntingtin poly-CAG mutation

Late presentation mimics that of neuro-degenerations of old age (*e.g.*, PD)

GENE MAPPING: HUNTINGTON'S DISEASE



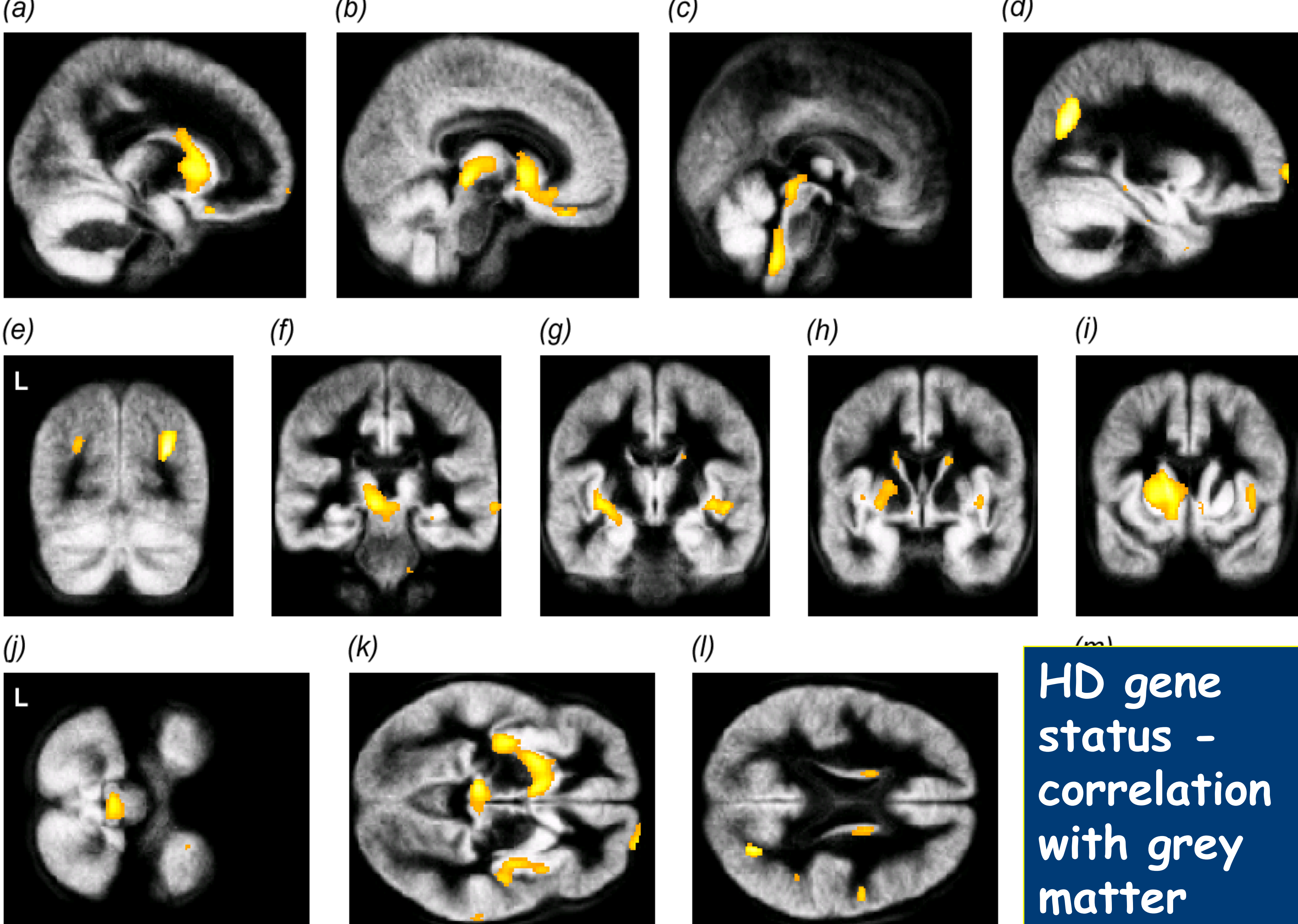
Design matrix for the grey matter gene status analysis.

Rows correspond to individual subjects, arranged by gene status - $cond_0$ and $cond_1$ are gene negative and positive.

A contrast of $cond_1$ and $cond_0$ identifies regions where grey matter is significantly reduced in gene-positive subjects

Controlled for differences in age, sex and global voxel intensity.

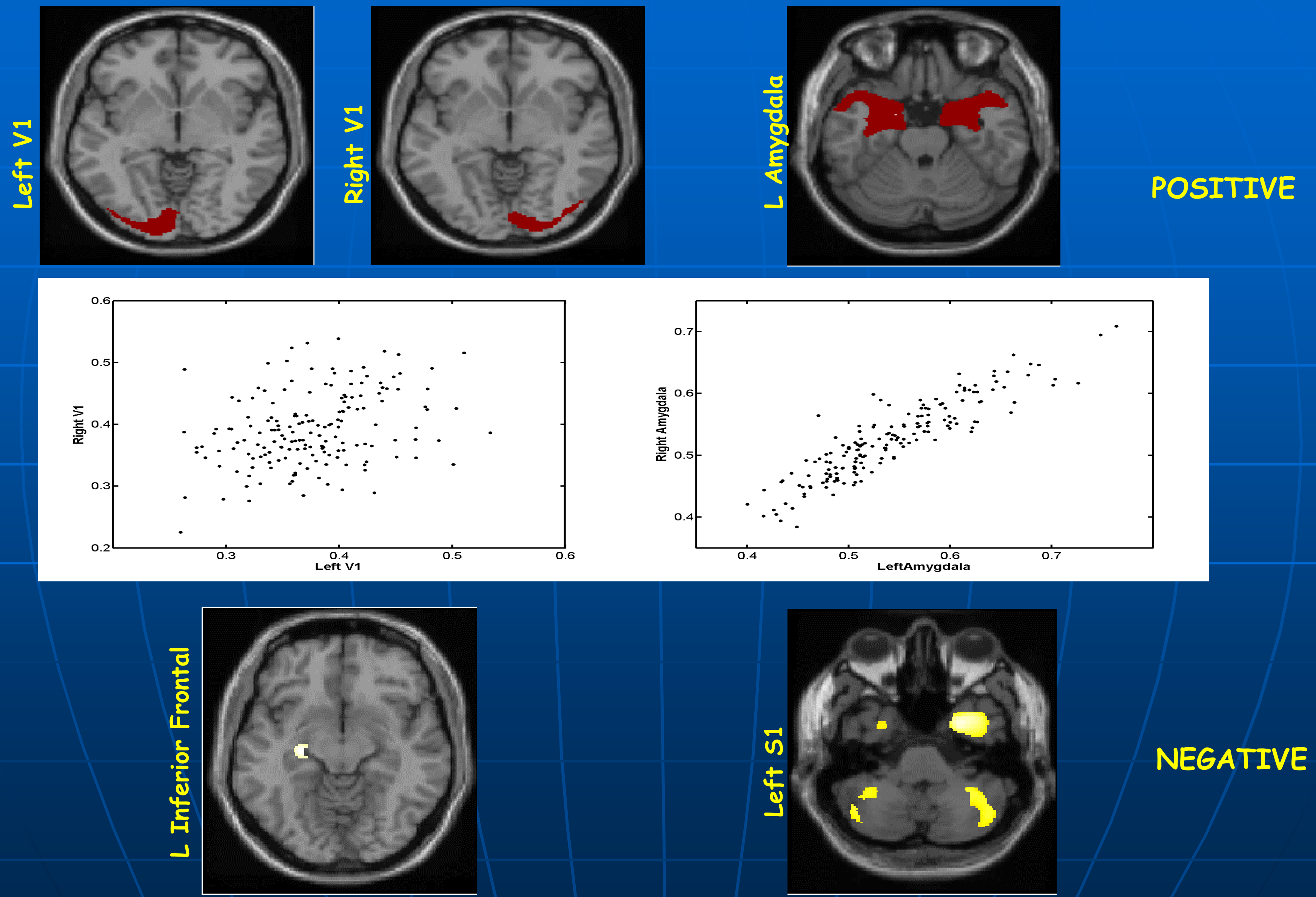
Structural biomarkers of preclinical disease



HD gene status - correlation with grey matter volume

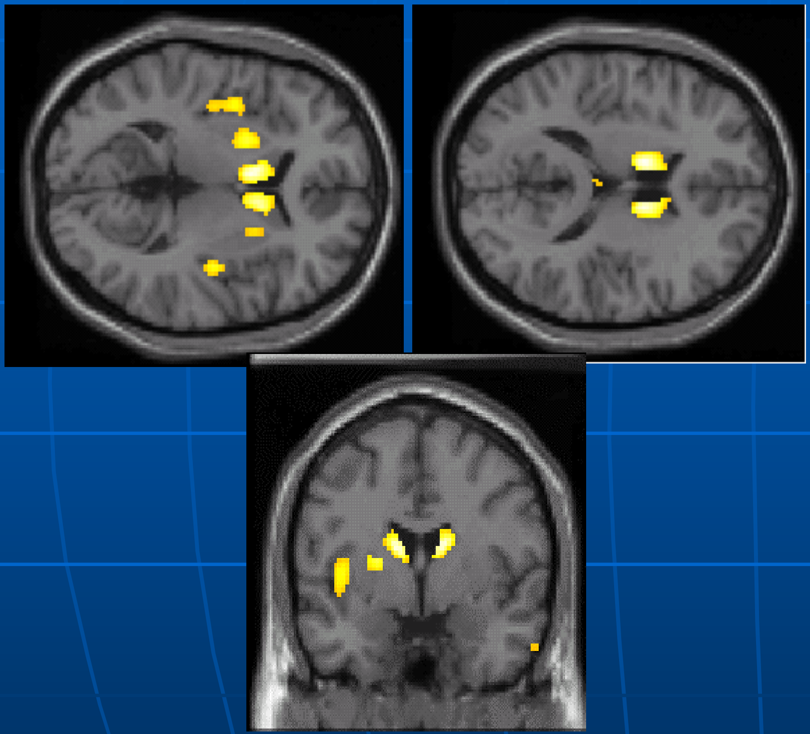
Structural biomarkers of preclinical disease

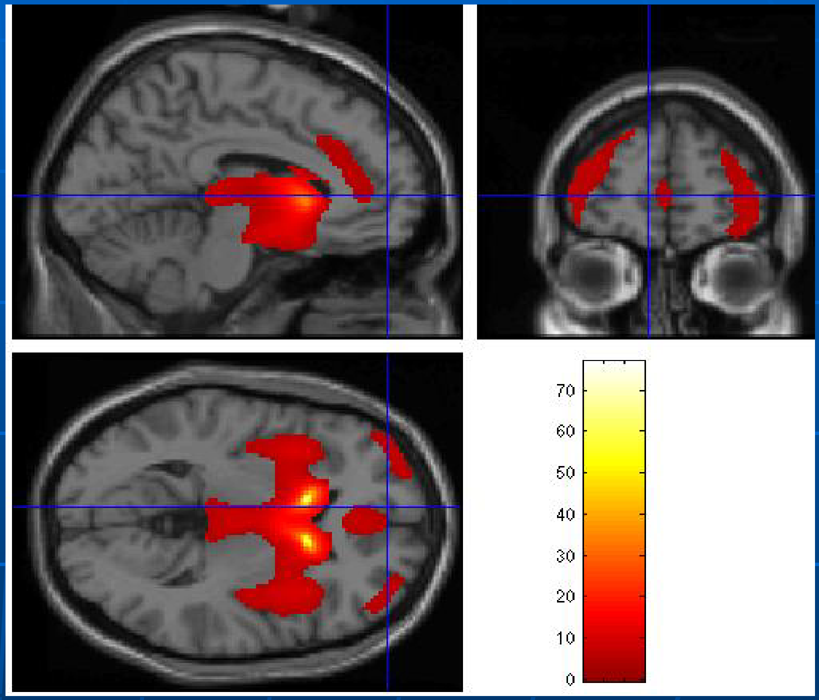
GREY MATTER CORRELATIONS BETWEEN HOMOTOPIC REGIONS



Structural correlations – structural systems

50 SUBJECTS WITH >36 CAG REPEATS COMPARED TO 50 WITH <32 CAG REPEATS





R

R

Structural biomarkers of preclinical disease

DELETION MAPPING

EXAMPLE:

TURNER'S SYNDROME

Model disease with total or incomplete deletion of X chromosome

Mild cognitive impairment indicates relevance of X-located genes in brain development

TURNER's SYNDROME

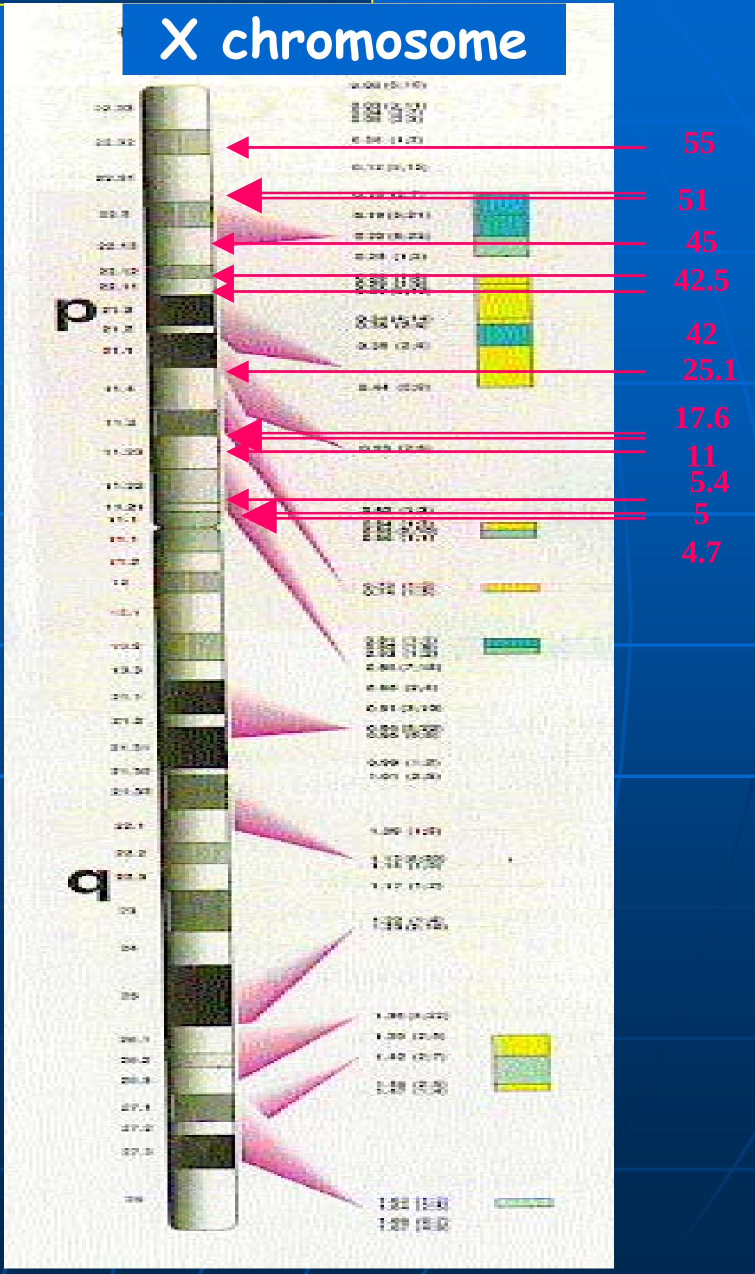
- **45,X0**

  complete deletion of X, non mosaic,
  - 10 F: maternal origin of X (23 ± 7 years)
  - 10 F: paternal origin of X (23 ± 7 years)

- **46,XXp-**

  gene mapped partial deletions
  - 12 F (25 ± 13 years)

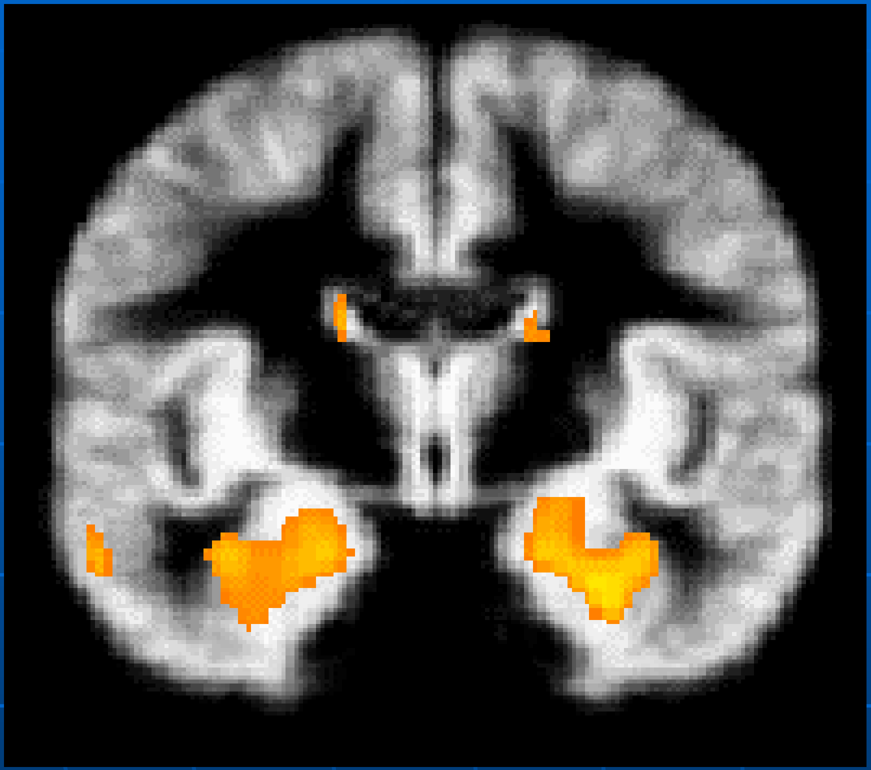
- **controls 46,XX**
  - 17 F (25 ± 9 years)
  - verbal IQ matched



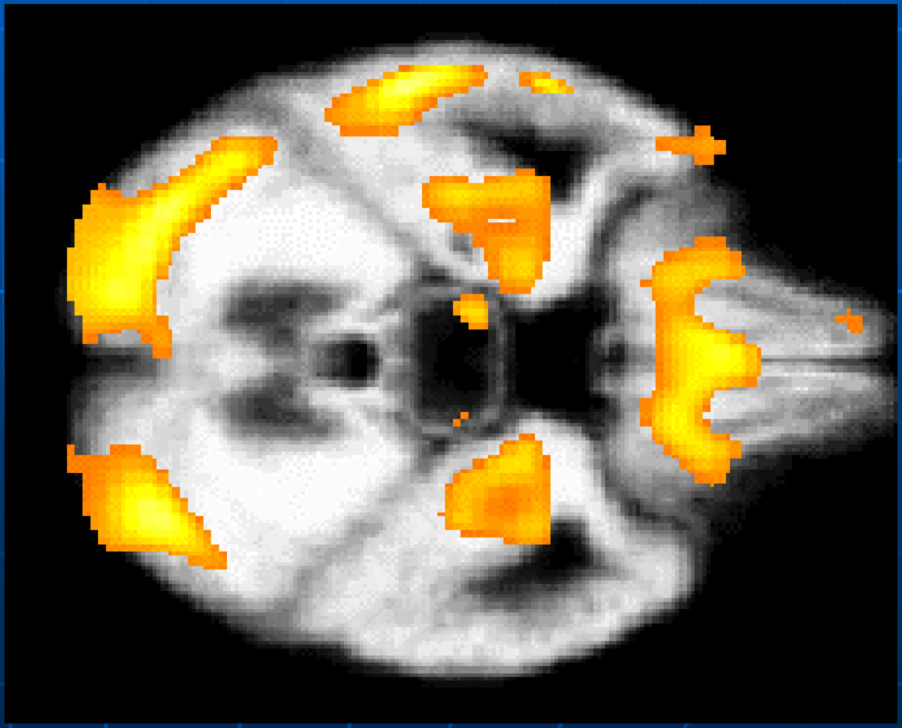
Cognitive & behavioural phenotype of the 45XO karyotype

- **Cognitive:**
  - normal verbal skills
  - impaired visuo-spatial and/or visuo-perceptual abilities
  - impaired visuo-constructive skills
  - mildly impaired motor function
- **Behavioural:**
  - social adjustment problems
  - some autistic features

VBM DETECTED CHANGES IN AMYGDALA AND ORBITO-FRONTAL CORTEX

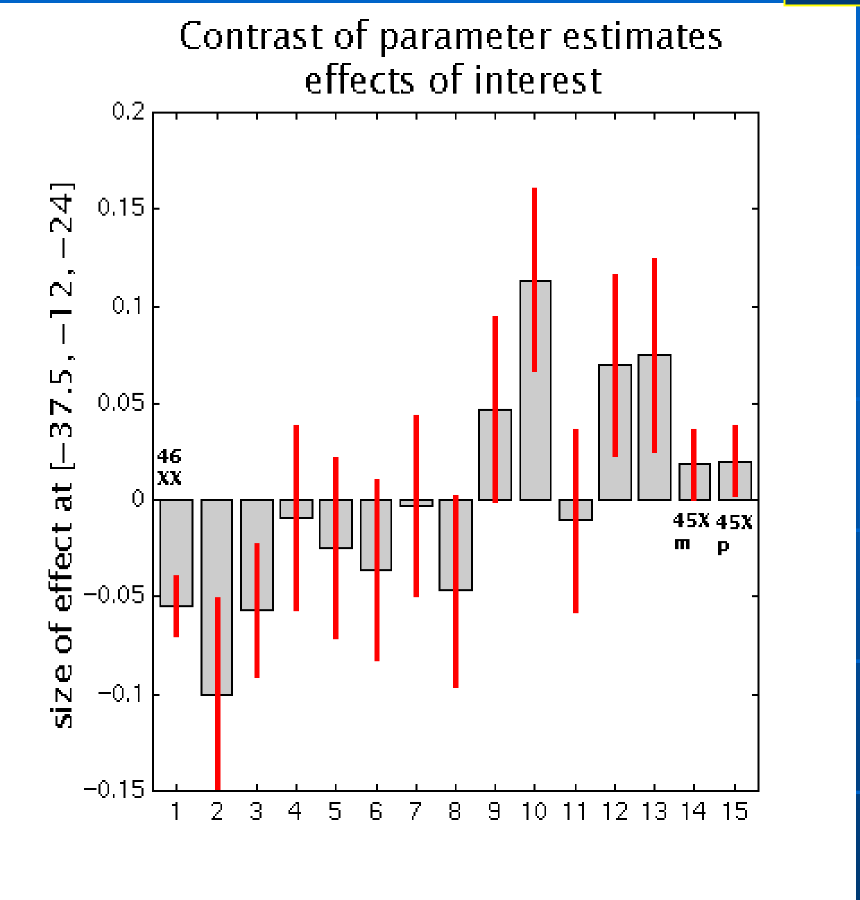


45,XO vs 46,XX

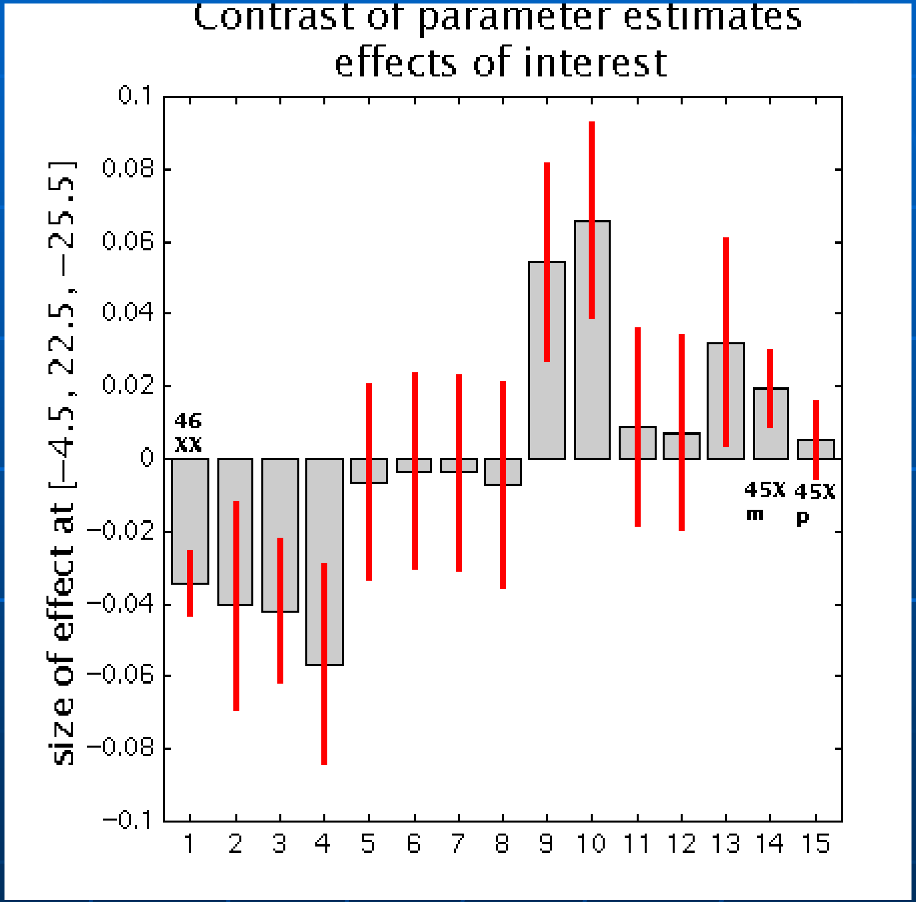


SIZES OF CEREBRAL REGIONS

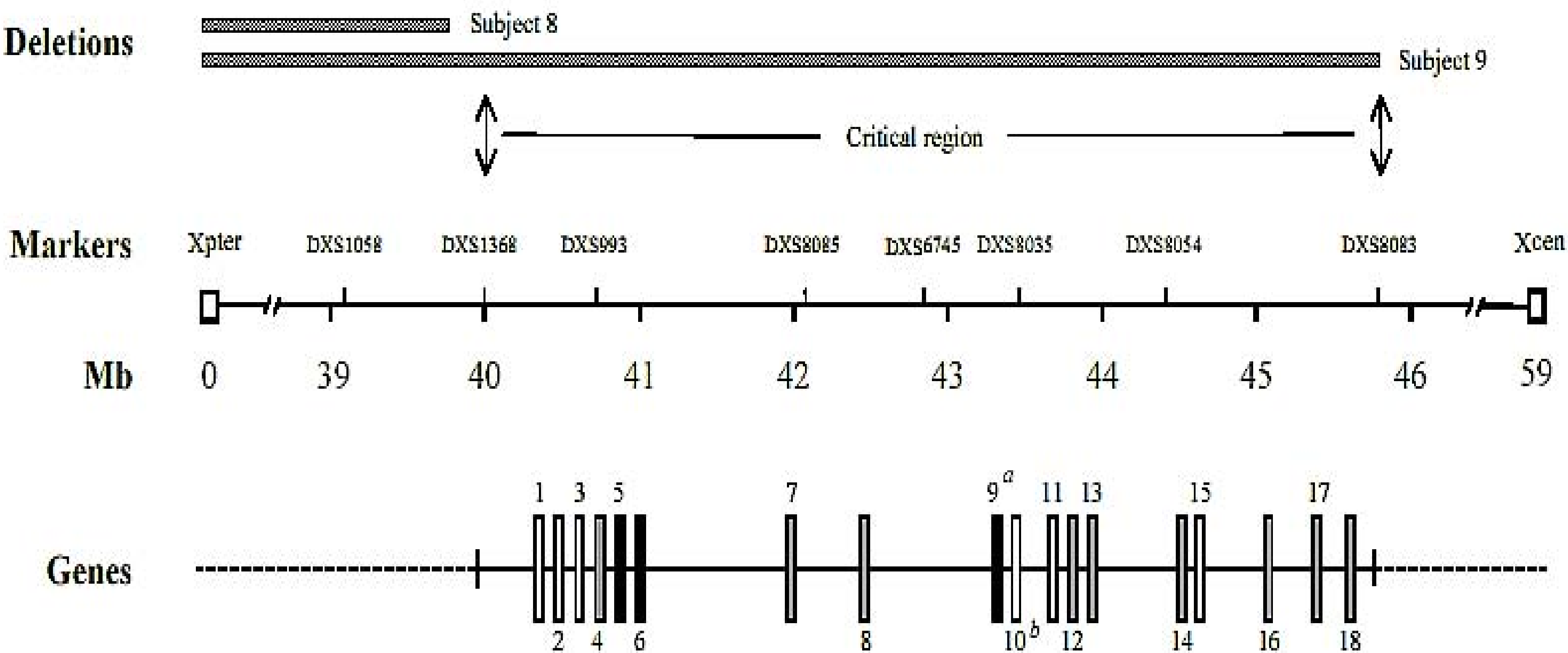
in relation to size of deletion



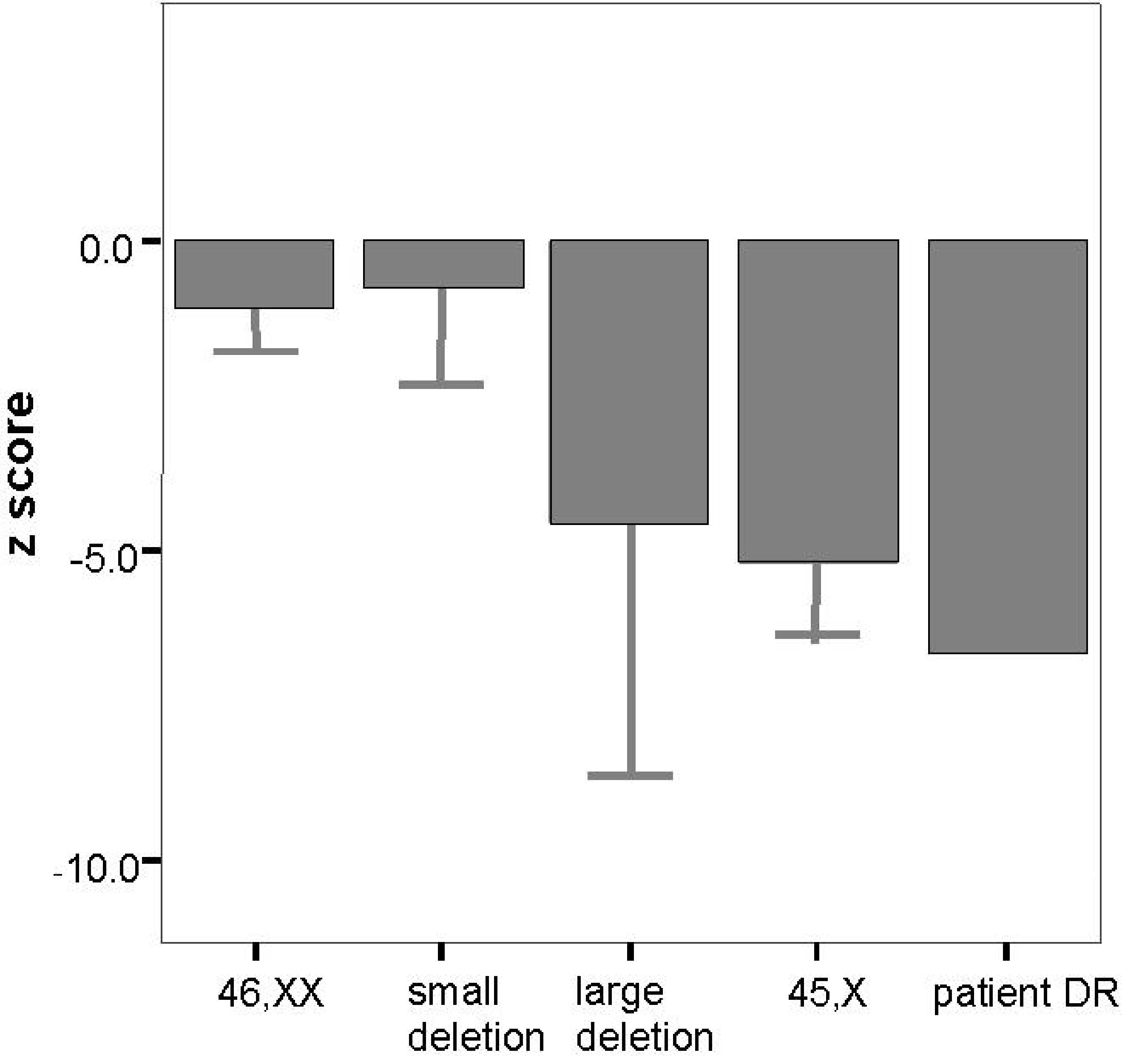
AMYGDALA



ORBITO-FRONTAL CORTEX


Deletions
Subject 8
Subject 9
Critical region
Markers
Xpter
DXS1058
DXS1368
DXS993
DXS8085
DXS6745
DXS8035
DXS8054
DXS8083
Xcen
Mb
0
39
40
41
42
43
44
45
46
59
Genes
1
2
3
4
5
6
7
8
9 a
10 b
11
12
13
14
15
16
17
18

MODIFIED BEHAVIOURAL PHENOTYPE



COGNITIVE & BEHAVIOURAL PHENOTYPE OF THE 45X0 KARYOTYPE

- **Cognitive:**
  - normal verbal skills
  - impaired visuo-spatial and/or visuo-perceptual abilities
  - impaired visuo-constructive skills
  - mildly impaired motor function
- **Behavioural:**
  - social adjustment problems
  - some autistic features
  - face and emotion recognition difficulties (fear & anger)

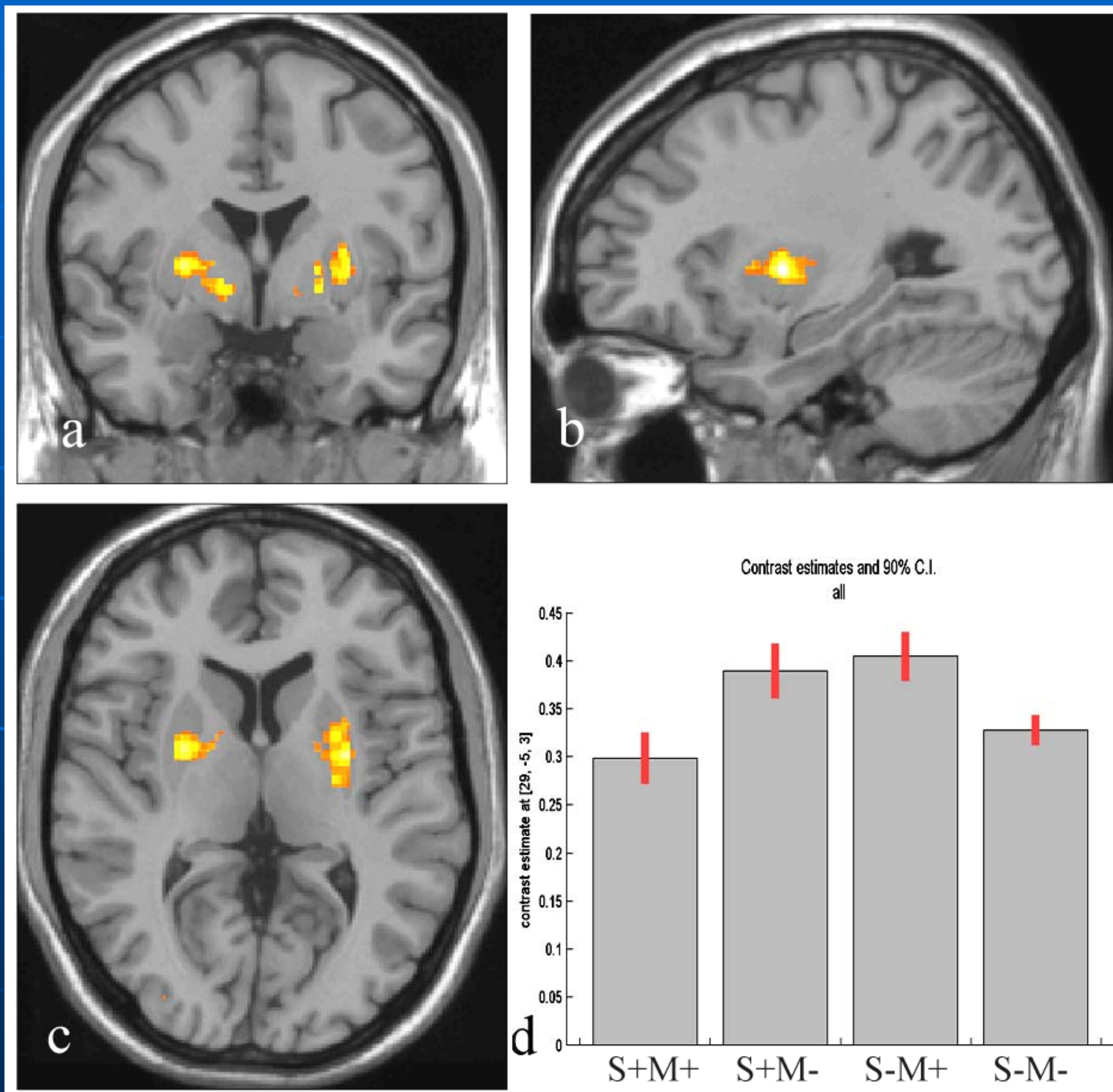
INTERACTIONS BETWEEN GENOTYPE AND PHENOTYPE

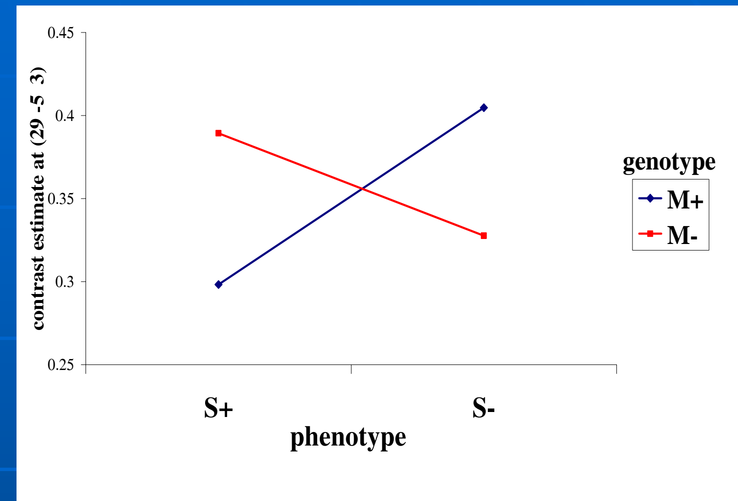
EXAMPLE:
SYMPTOMATIC DYSTONIA

Early onset common variety associated with DYT1 mutation, dominant inheritance but incomplete penetrance – 40%

Non dystonics with/without DYT1 mutation
Dystonics with/without DYT1 mutation

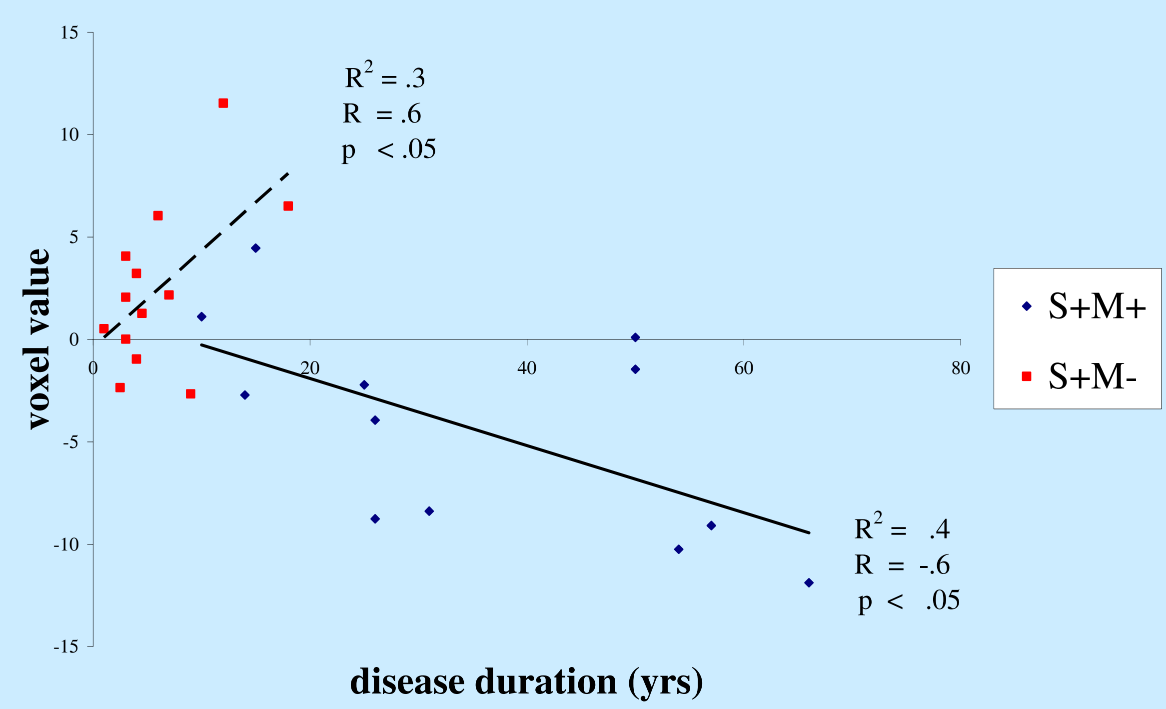
MUTATION-PHENOTYPE INTERACTION - DYSTONIA





		GENOTYPE	
		M+	M-
PHENOTYPE	S-	S-M+	S-M-
	S+	S+M+	S+M-

DYT1 GENE MUTATION

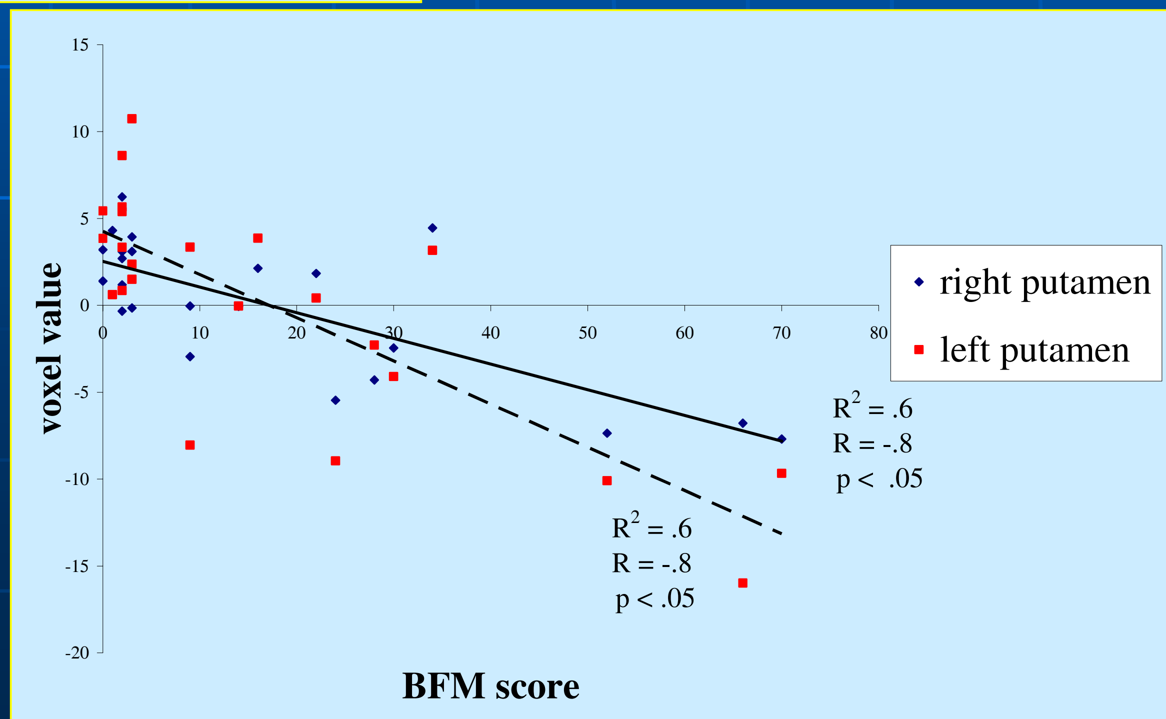


SYMPTOMATIC DYSTONIA

S+M+ and S+M-

MUTATION CARRIERS

S+M+ and S-M+



PARTITIONING THE EFFECTS OF PREDISPOSING GENES

EXAMPLE:

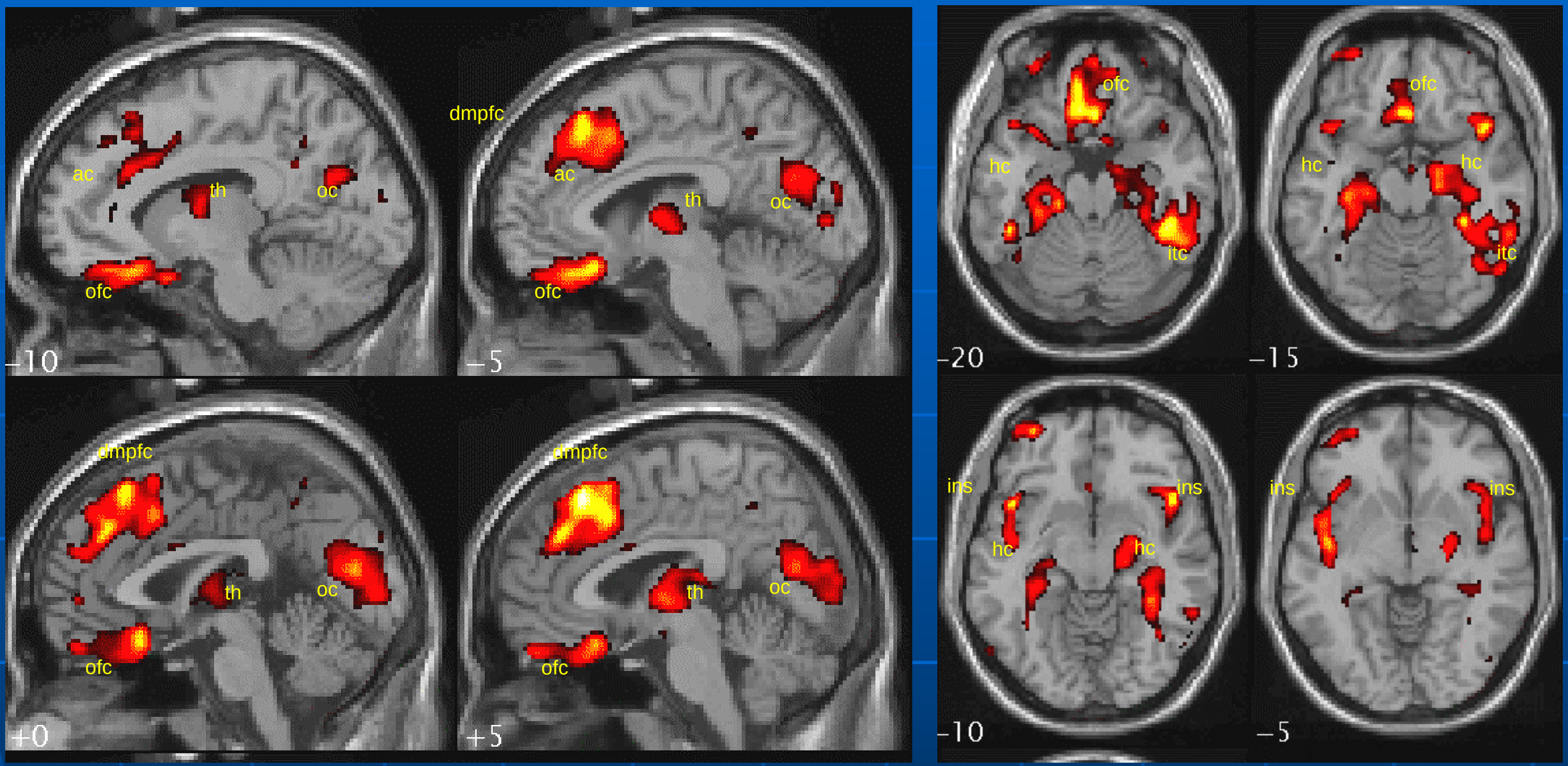
SCHIZOPHRENIA

Transmission dysequilibrium of Chr 8 polymorphisms in families and allelic association in case control and trio studies - PCM1 8p22

Non-schizophrenics with/without predisposing polymorphism

Schizophrenics with/without predisposing polymorphism

GREY MATTER ATROPHY ASSOCIATED WITH SCHIZOPHRENIA PHENOTYPE

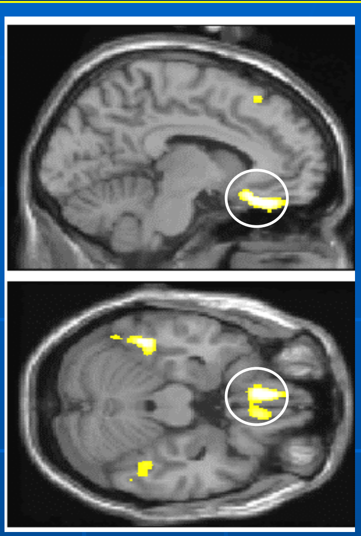


ATROPHY ASSOCIATED with SCHIZOPHRENIA

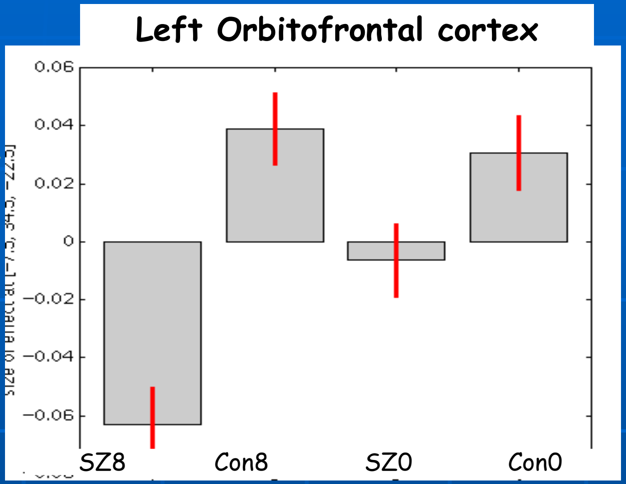
SZ8 & SZ0 compared to CONTROLS (CON8 & CON0)

ac	anterior cingulate
dmpfc	dorsal medial prefrontal cortex
ofc	orbitofrontal cortex
th	thalamus
oc	occipital cortex
hc	hippocampus
ins	insula
itc	inferior temporal lobe

GREY MATTER ATROPHY ASSOCIATED WITH ALLELIC-SCHIZOPHRENIA INTERACTION

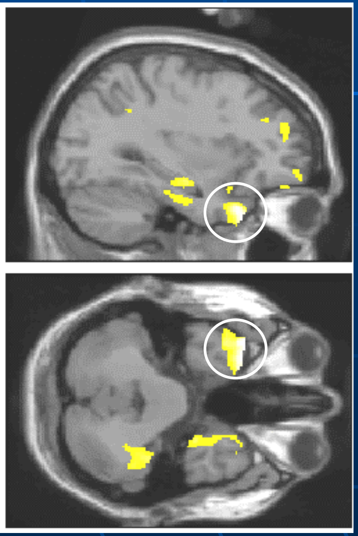


Effect size

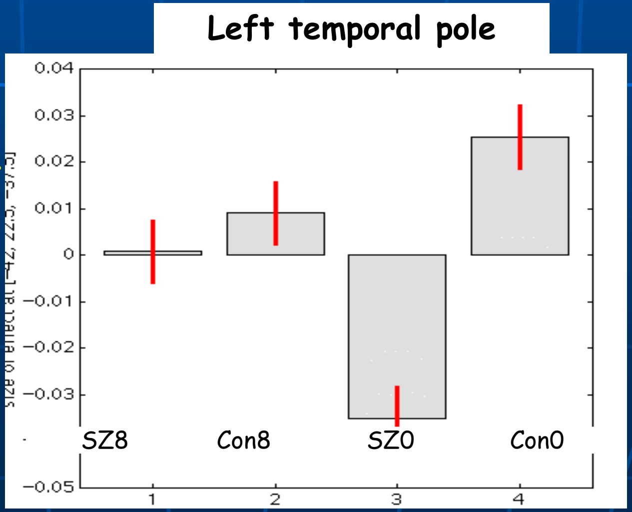


SZ8

x,y,z -7.5,34.5.-22.5
Interaction, F=4.6,
p<0.05



Effect size



SZ0

x,y,z -42.0,22.5,-37.5
Interaction, F=12.7,
p<0.01

Genetics and structural variability

SCIENCE

POPULATION SAMPLES

GENERALISABLE INFERENCES

COMPARISONS & CORRELATIONS

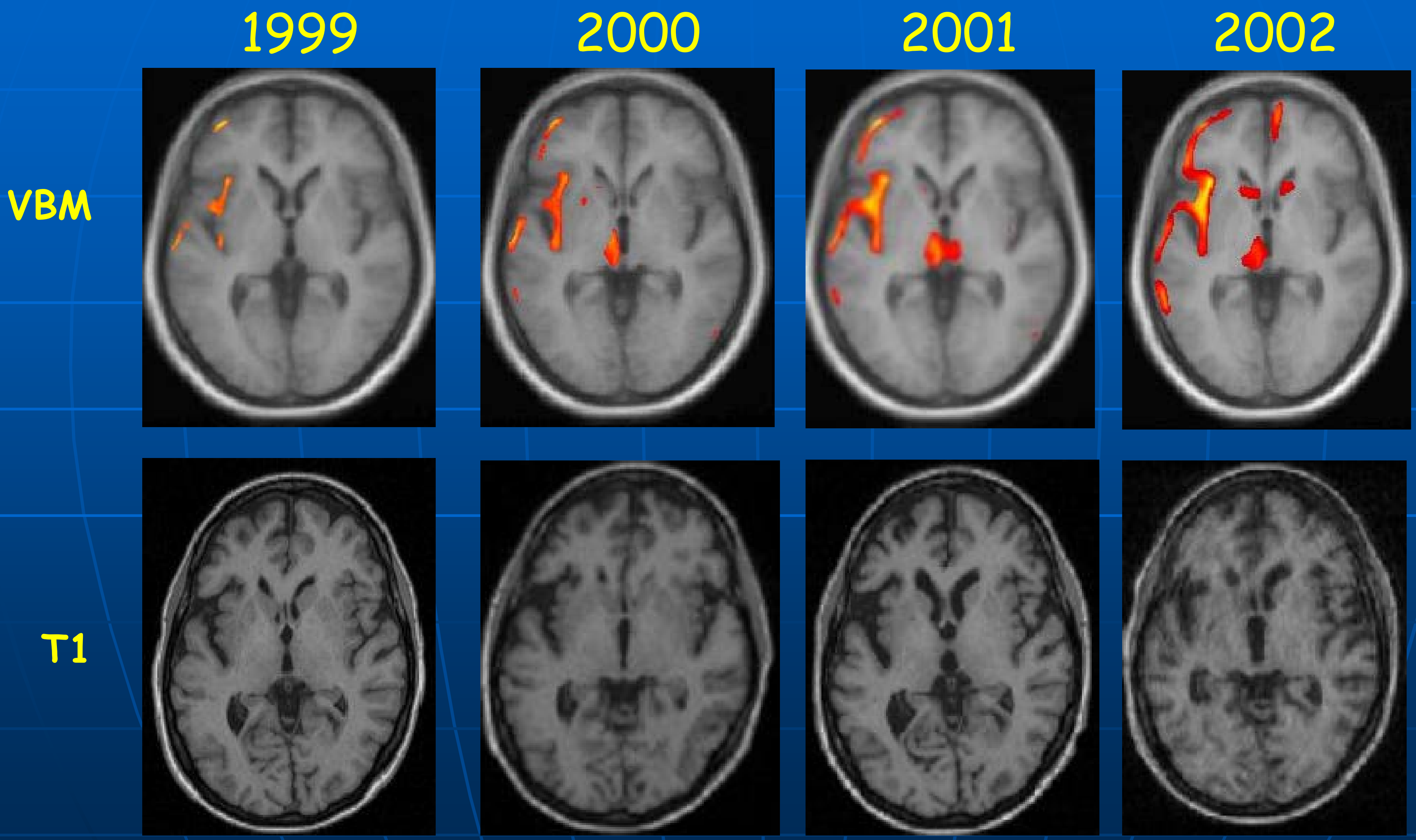
MEDICINE

INDIVIDUAL PATIENTS

DIAGNOSIS AND PROGNOSIS

CLASSIFICATION

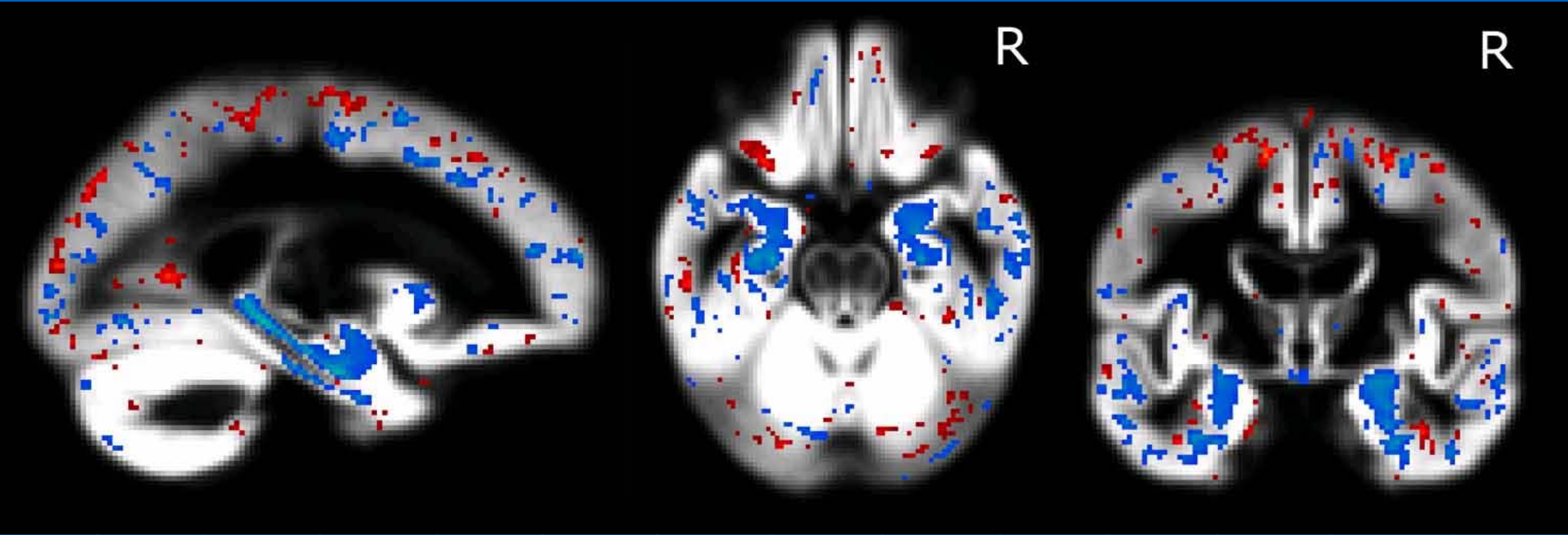
STRUCTURAL EVOLUTION OF DEMENTIA



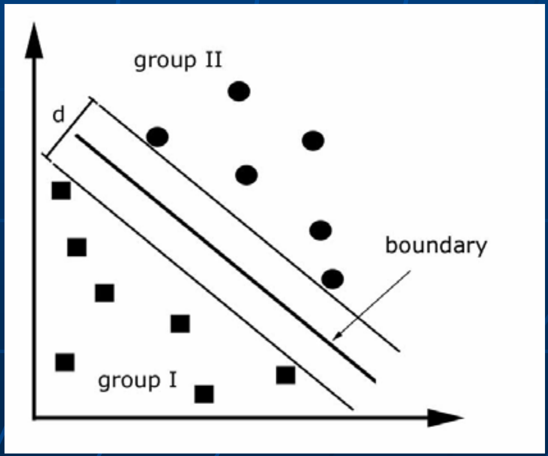
Courtesy M-L Gorno-Tempini

Structural biomarkers of preclinical disease

ILLUSTRATION OF VOXELS MOST RELEVANT FOR THE DIFFERENTIATION OF PATIENTS FROM CONTROLS.



CLASSIFICATION USING MACHINE-LEARNING TECHNIQUES INCLUDE SUPPORT VECTOR MACHINES AND RELEVANCE VECTOR REGRESSIONS



CLASSIFICATION OF INDIVIDUAL SCANS USING SVM

Group	% correctly classified	Sensitivity (%)	Specificity (%)
AD (MMSE 15-27) and controls (MMSE 28-30)	82.9	79.4	85.9
AD (MMSE 15-30) and controls (MMSE 26-30)	82.2	80.0	84.3
AD (MMSE 20-30) and controls (MMSE 26-30)	80.3	69.0	87.6

WHOLE BRAIN

Group	% correctly classified	Sensitivity (%)	Specificity (%)
AD (MMSE 15-27) and controls (MMSE 28-30)	90.4	86.8	93.6
AD (MMSE 15-30) and controls (MMSE 26-30)	87.6	86.3	88.8
AD (MMSE 20-30) and controls MMSE 26-30)	87.0	81.0	91.0

MEDIAL TEMPORAL REGIONS

THANKS TO:
B Draganski
S Kloppel
C Stonnington
J Ashburner
A Mecheli
C Good
H Gurling
S Ramsay

THE END

Proton Radiosurgery
Past, Present, and Future

Reinhard W. Schulte, M.D.
Proton Treatment Center
Loma Linda University Medical Center

Objectives

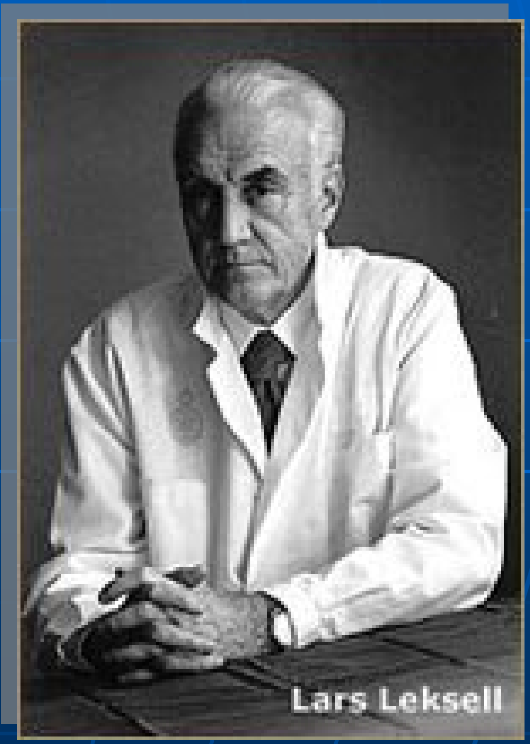
- Understand the use of protons in the historical context of radiosurgery
- Understand physical characteristics of protons and how they relate to Bragg-peak and plateau radiosurgery
- Introduce the Proton Radiosurgery Program at LLUMC
- Present current R&D activities in Functional Proton Radiosurgery

Outline

- The Beginnings and Development of Radiosurgery
- Protons and other Modalities for Radiosurgery
- Proton Radiosurgery: Plateau versus Peak
- Bragg Peak Radiosurgery
- Development of Plateau Radiosurgery
- Conclusions and Future

A Man – A Vision

- In 1951 Swedish neurosurgeon Lars Leksell (1907-1986) suggested*:
  - To create functional brain lesions with multiple narrow radiation beams converging on one point
  - To use stereotactic techniques to guide the beams
  - To call this technique "stereotaxtic radiosurgery"



*L. Leksell
The stereotaxic method and radiosurgery of the brain.
Acta Chir Scand. 102:316-9, 1951.

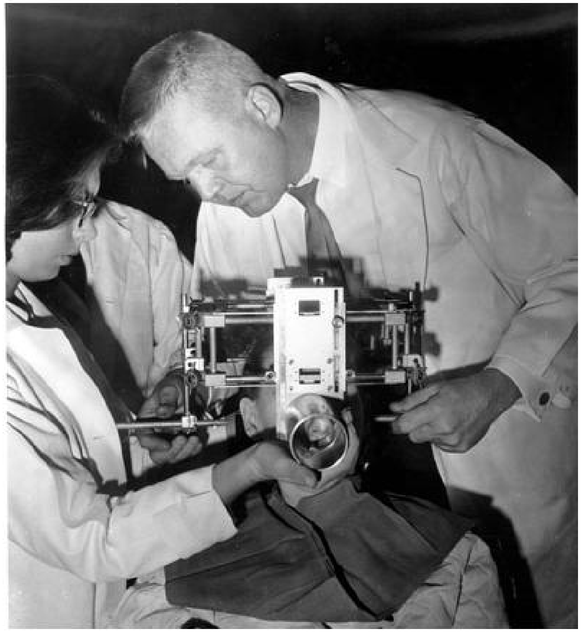
The Early Years of Particle Therapy (1948-1955) Lawrence Berkeley Laboratory

- Starting in 1948, John Lawrence (physician) and Cornelius Tobias (biophysicist) developed biomedical program of heavy ions at the LBL cyclotrons
- In 1954, the LBL group began to direct the Bragg peak of heavy ion beams (protons & helium) at human pituitary glands (about 50 patients)
- Reported successful hormonal ablation & regression of disease in advanced breast cancer patients

CORNELIUS "TOBY" TOBIAS

Radiosurgery Program at the Harvard Cyclotron Laboratory 1961-2001

- In 1961, neurosurgeon Raymond Kjellberg began treating patients with pituitary adenomas using 160 MeV Bragg peak protons from the Harvard Cyclotron Laboratory
- Starting in the 1970s, Dr. Kjellberg also treated large, inoperable arteriovenous malformations (AVMs) with Bragg peak protons, despite limitations in imaging and planning techniques



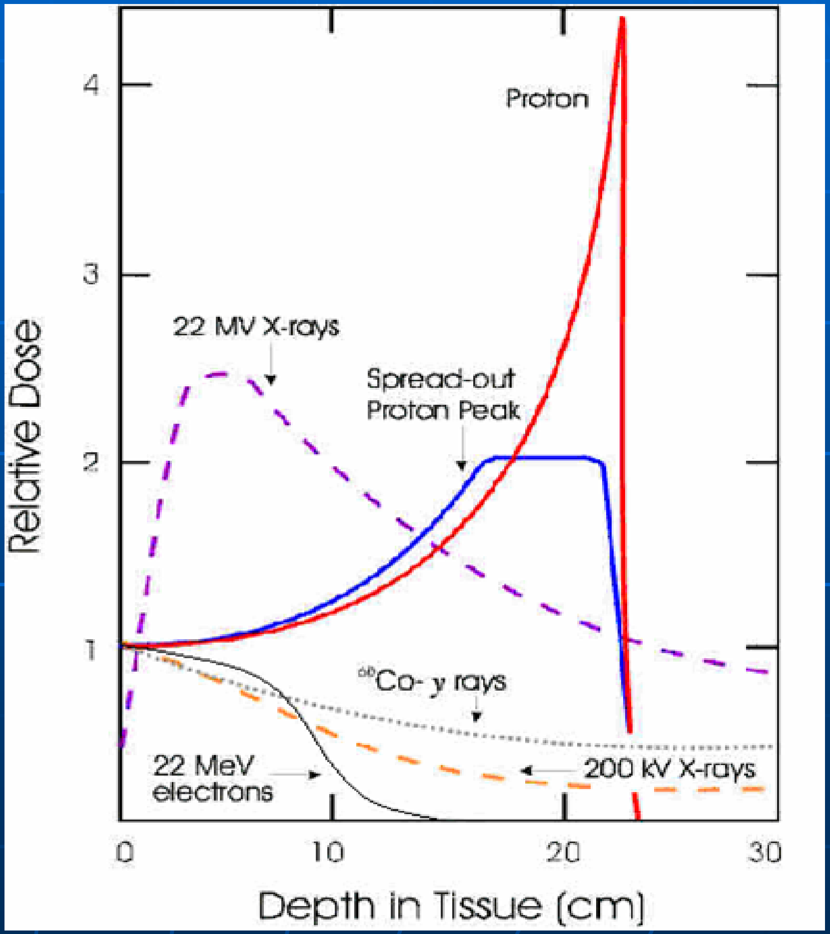
Raymond Kjellberg, MD

Which Radiation for Radiosurgery?

- Principal modalities include
  - Photons
    - High energy gamma rays (e.g. ^{60}Co)
    - High energy photons (linear accelerator)
  - Charged particles
    - Protons
    - Heavy ions (helium, carbon)
- Important points to consider
  - Depth-dose characteristics
  - Lateral profile
  - Beam Fragmentation

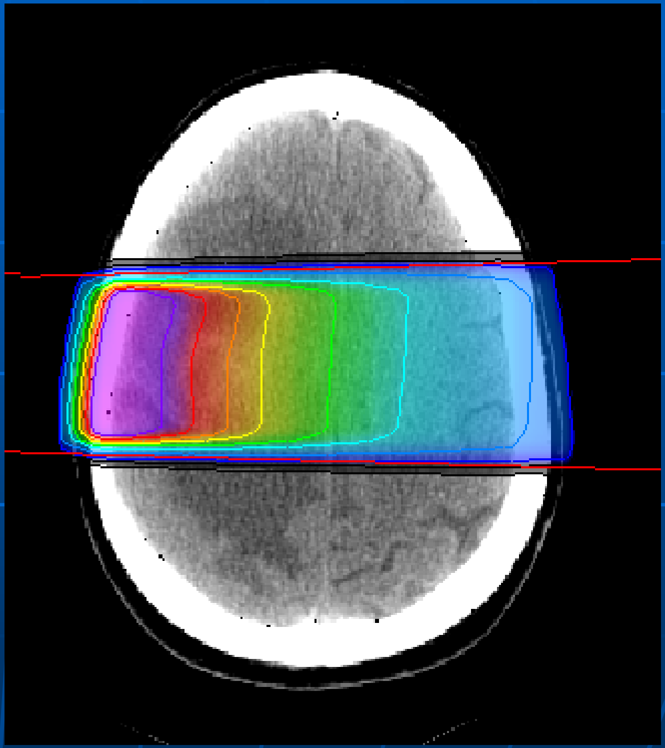
Depth-Dose Characteristics

- Inverted dose profile of protons and heavy ions
  - Low entrance dose (plateau)
  - Maximum dose at depth (Bragg peak)
  - Rapid distal dose fall-off
  - Energy modulation (Spread-out Bragg peak)
  - RBE close to unity



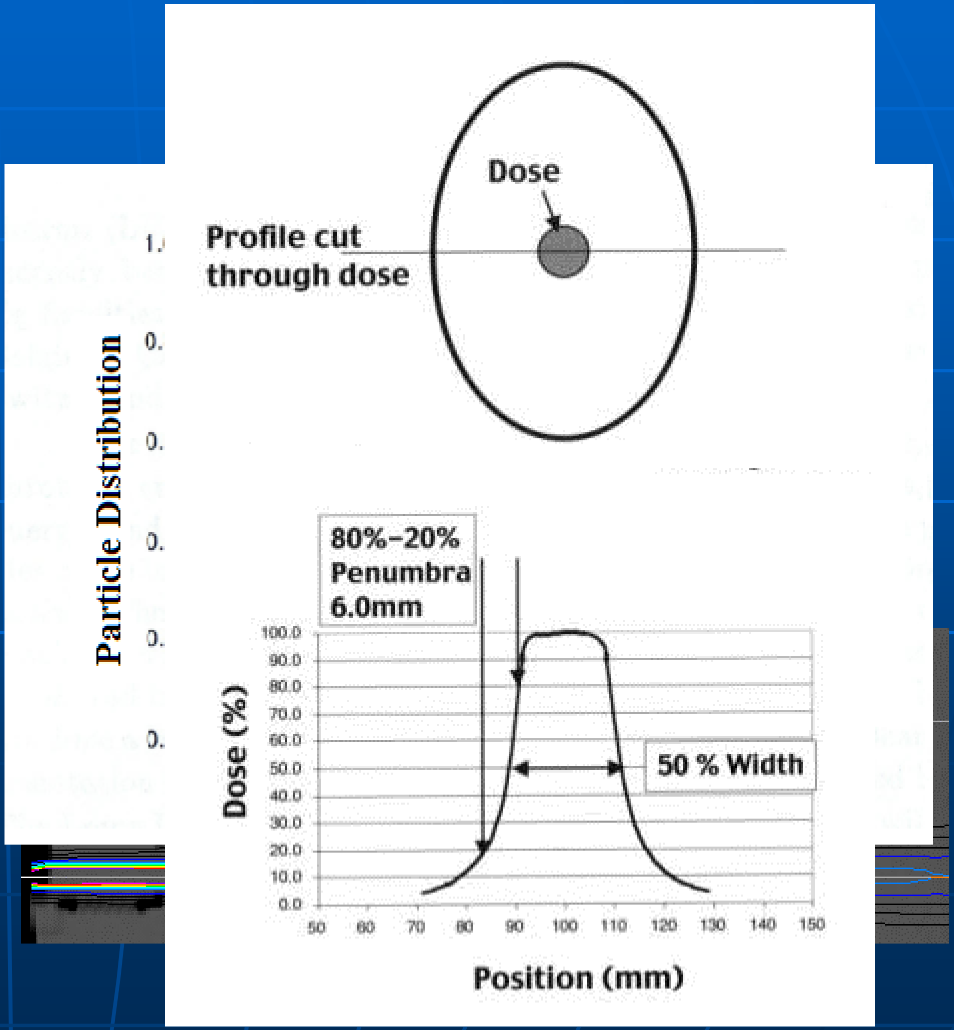
Advantages of Protons in Conformal Radiosurgery

- The depth-dose characteristics of protons and heavy ions favor their use in conformal radiosurgery
- Advantages include
  - Less integral dose
  - Smaller number of individual beams
  - Higher degree of conformality for large lesions
  - No need for multiple isocenters



Lateral Profile

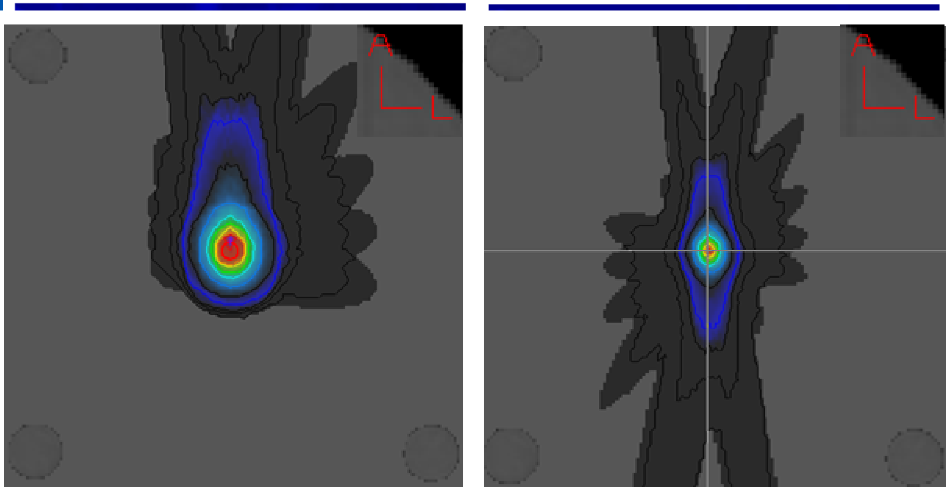
- Important for sparing nearby critical structures
- Protons vs. helium: heavier ions have less scattering
- Particle energy: higher energies achieve sharper profiles



Lateral Profile

- Protons vs. Gamma
  - Protons of high energy (250 MeV) have sharper penumbra than gamma knife beams for depths below 10 cm
  - Protons of high energy can produce smaller beams (= lesions) than the smallest GK beams
  - Protons of energy less than 200 MeV are less suitable for functional radiosurgery beams

Penumbra (20%-80%) of a 4-mm collimated proton beam

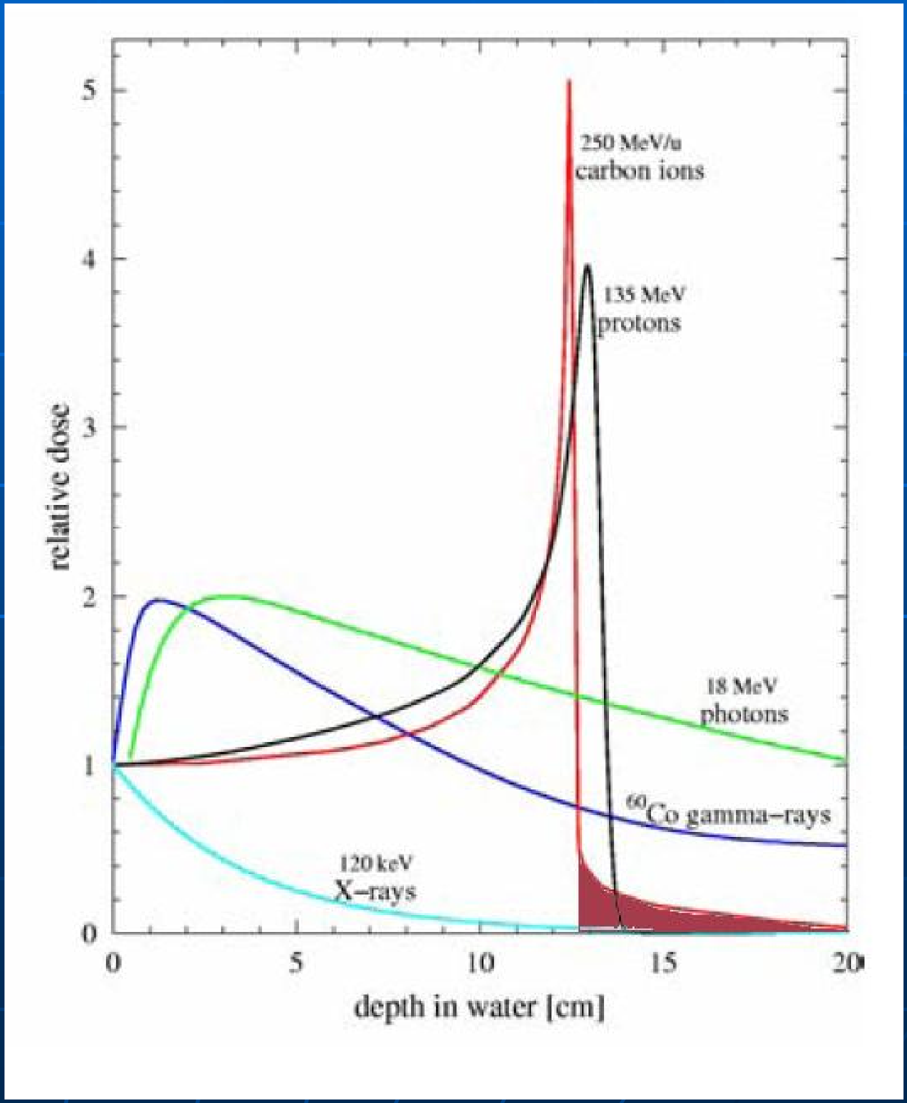


155 MeV Bragg Peak, 2.5 mm

250 MeV, Plateau, 2.5 mm

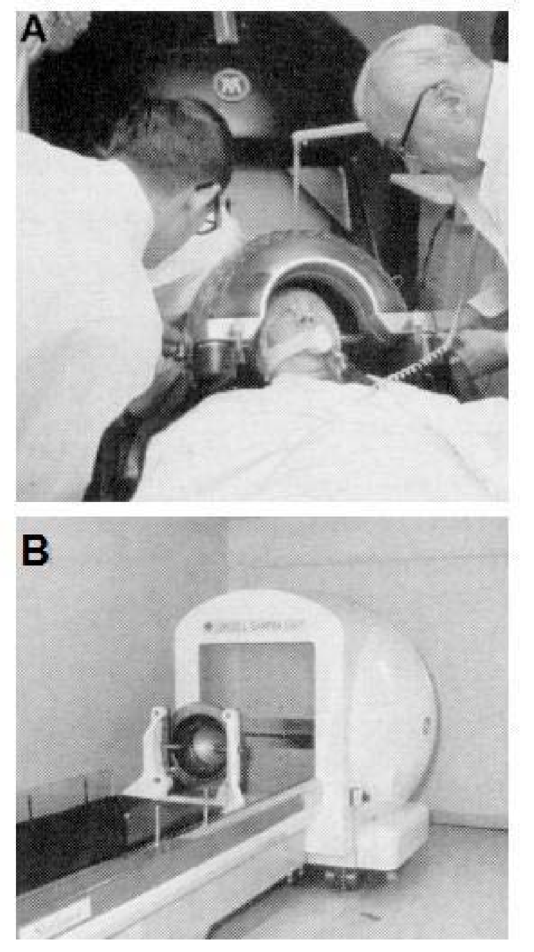
Fragmentation

- Charged particles can cause fragmentation of target nuclei in nuclear interactions
- Particles heavier than protons can break up in to fast lighter fragments
- These deliver dose beyond the Bragg peak (fragmentation tail)



Why Leksell chose Gamma Rays and not Protons

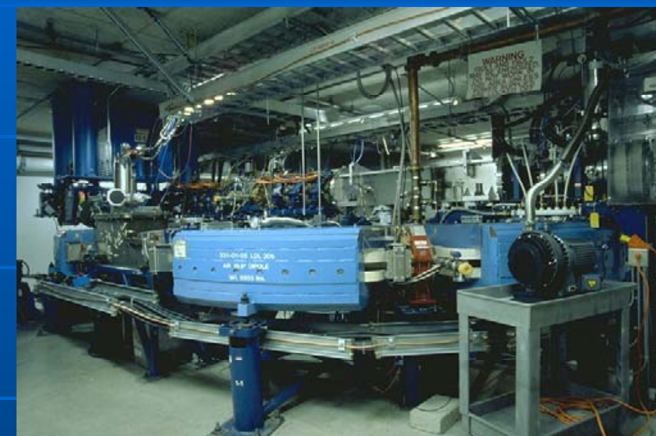
- Leksell, working with physicist Borje Larsson, at first used dental orthovoltage X-rays for radiosurgery
- Realizing limitations, they looked into other modalities including protons
- Due to limited availability of protons (which would have been the preferred choice) attention focused on the gamma knife instead



A Leksell and Larsson
B The first Gamma Knife

LLUMC Proton Treatment Center 1990 - present

Hospital-based facility



40-250 MeV Synchrotron

Gantry beam line

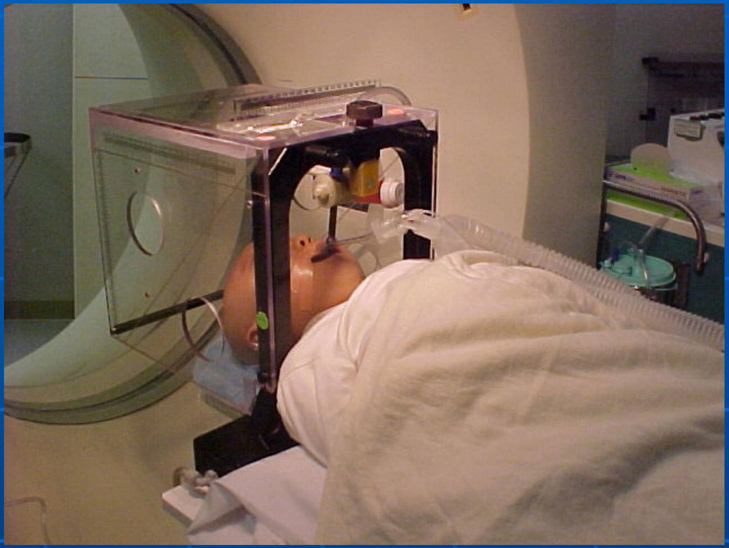
Fixed beam line

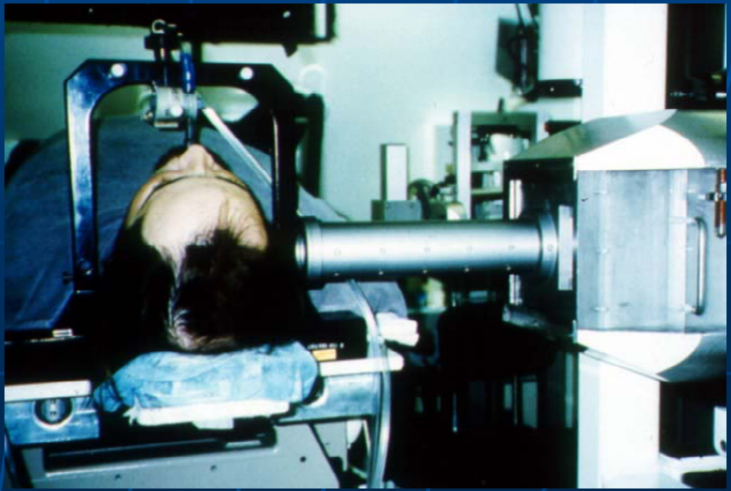
Stereotactic Proton Radiosurgery Program at LLUMC

- Bragg Peak Radiosurgery (since 1993)
  - Single-dose proton radiosurgery and two-fraction stereotactic proton radiotherapy to create highly conformal dose distributions with the Bragg-peak
    - Arteriovenous malformations
    - Brain metastases
    - Other intracranial tumors (re-treatment etc.)
    - Mesial temporal lobe epilepsy
- Plateau Radiosurgery (under development)
  - Single-dose functional proton radiosurgery with plateau shoot-through beams
    - Trigeminal neuralgia, Thalamotomy, Callosotomy

Bragg-Peak Proton Radiosurgery/therapy Technique

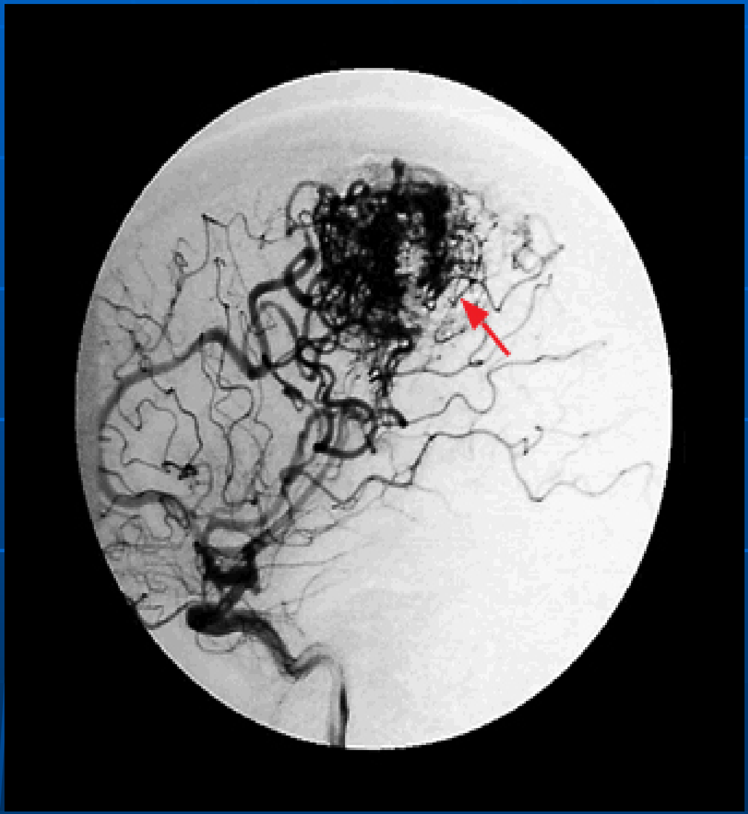
- Non-invasive fixation based on dental vacuum
- Treatment planning based on CT, CTA, MRI, MRA, PET
- Treatment in one-three fractions based on location and size





Arteriovenous Malformations

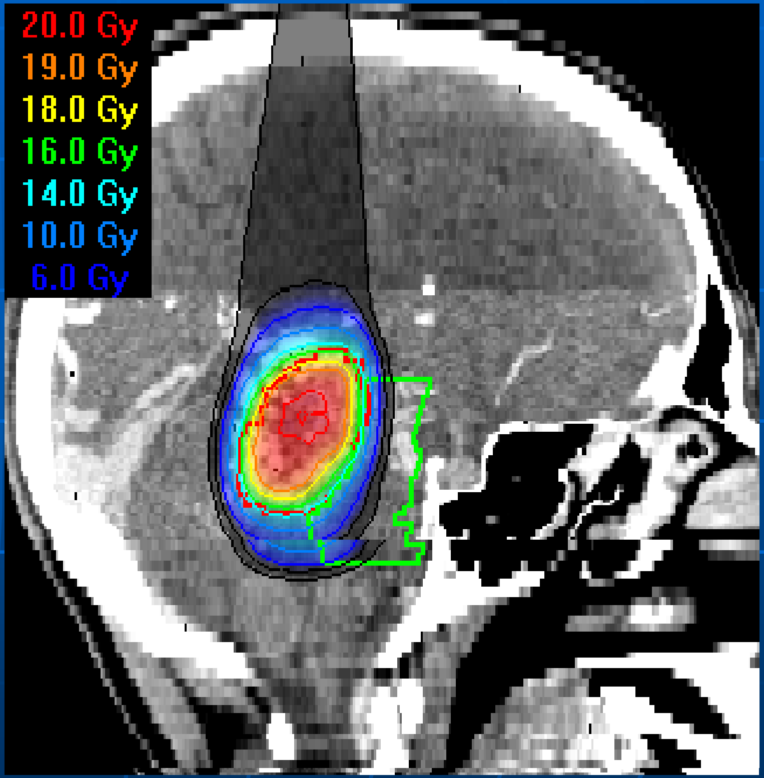
- Most dangerous congenital vascular malformation
- Patient present with intracranial hemorrhage, seizures, headaches, and/or neurological deficits
- Peak-age: 10-40 years
- Large AVMs require multidisciplinary approach (surgery, endovascular therapy, and radiosurgery)
- Curative doses >16 Gy single dose, >20 Gy 2 fx
- Proton SRS/SRT has been used as part of interdisciplinary therapy and as primary treatment modality in inoperable AVMs



Characteristic angiographic appearance of an arteriovenous malformation

AVM Treatment Example

- 17 y/o female with a relatively large AVM of the tectal plate invading the midbrain; s.p. four endovasclar treatments => partial obliteration
  - Aim of therapy: Curative proton SRT in 2 fractions
  - Immobilization: vacuum-assisted dental fixation, stereotactic frame
  - Dose planning: CT, CT-angio, MRI and MRA of the head
  - Prescribed dose: 20 GyE to isocenter, 16 GyE (80%) to margin of the nidus, 2 consecutive tx days, exclude brain stem
  - Organs at Risk: Brain stem (dose limit 15 GyE, 2 fx to surface)
  - Technique:
    - Four non-coplanar fields (RPO, LPO, RSO, LSO)



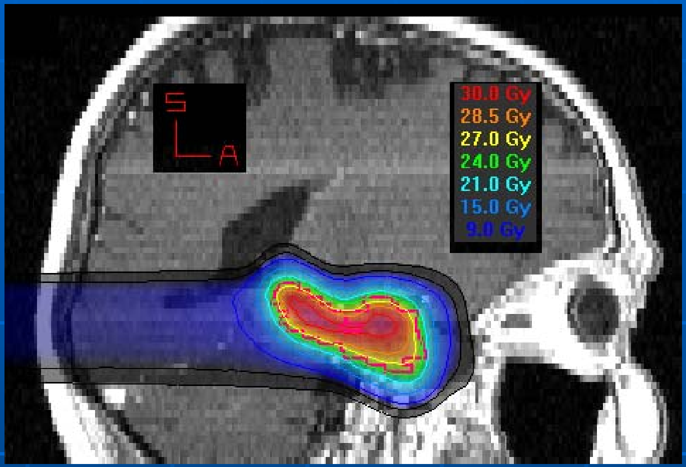
Isodose plan of patient with AVM

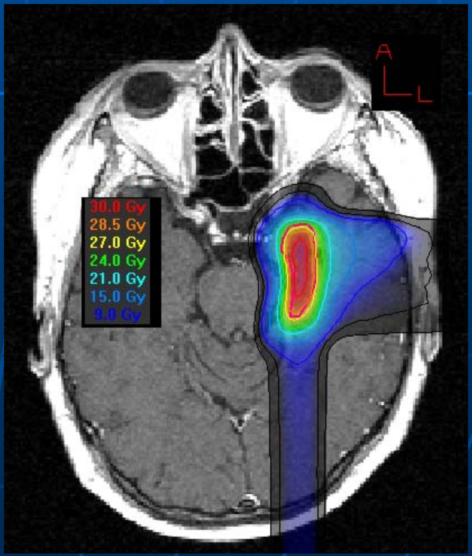
Proton Radiosurgery of Epilepsy

- Protocol under development for selected patients with mesial temporal lobe epilepsy (MTLE)
- Based on existing clinical experience with Gamma Knife radiosurgery
- Rationale:
  - Improved normal tissue sparing, less toxicity
  - Homogeneous dose distribution
  - Less integral dose, lower risk of secondary cancer

Proton Radiosurgery of Epilepsy Treatment Technique

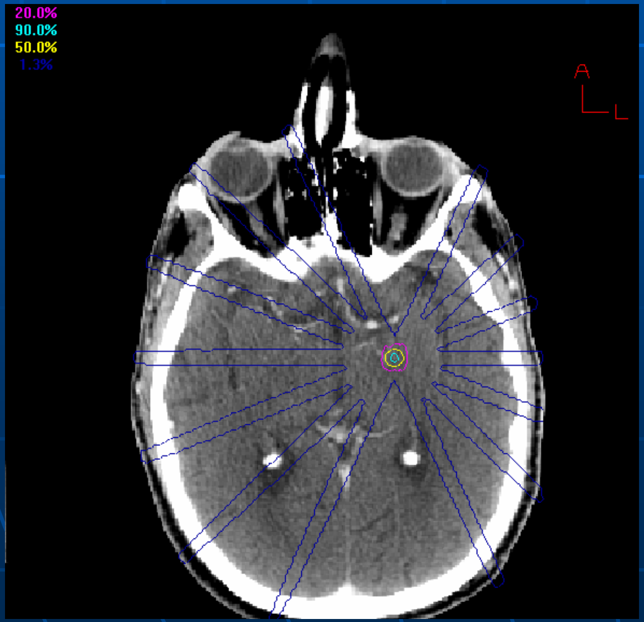
- Inclusion & exclusion criteria as defined by GK Multi-Center Trial
- Single-dose Bragg-peak radiosurgery (Leksell frame)
- Marginal isodose: 24 GyE
- Maximum dose $\leq$30 GyE

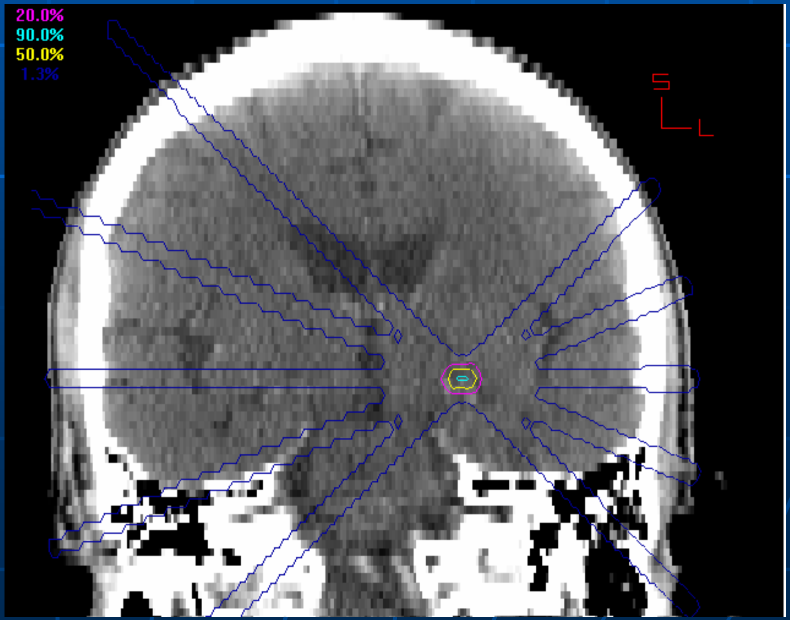




Development of Plateau Proton Radiosurgery for Functional Disorders

Tools used by the surgeon must be adapted to the task, and where the brain is concerned, they cannot be too refined.
Lars Leksell





Plateau Proton Radiosurgery Advantages and Challenge

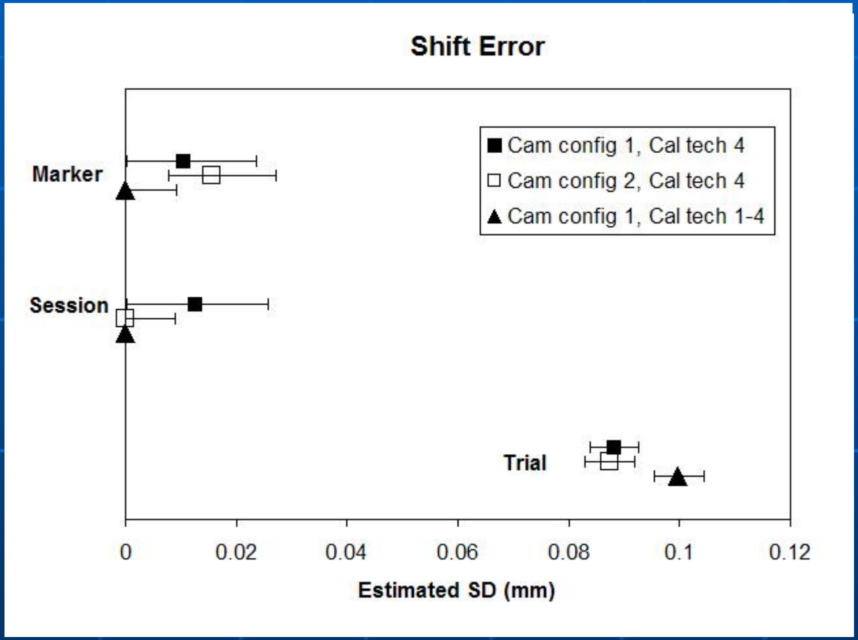
- Advantages
  - Plateau proton beams are sharper than Gamma knife beams if the target is not too deep (<10 cm)
  - Plateau proton beams can be made smaller (1-3 mm) than the smallest Gamma knife beams (4mm)
- Challenge
  - Maintaining all beams focused within 0.3 mm (GK standard) with a rotating proton gantry (3 stories, 100 tons) in combination with a robotic patient positioner is an engineering challenge

Optoelectronic System for Monitoring Brain Lesioning with Proton Beams

- Versatile system for anatomical lesioning used both in clinical and animal research applications
- Optoelectronic tracking of target and proton gantry in real time

Optoelectronic System Performance Study

- Endpoints (repeated tracking of 15 markers 1.1 m from cameras)
  - Distance of each markers from center of gravity of all others
  - Measured displacement after prescribed microstage shifts
- Results
  - Mean CG distance errors ~0.1 mm, SD 0.16 mm to 0.21 mm
  - Mean shift error < 0.01 mm, SD 0.014 mm to 0.022 mm



F. Shihadeh et al. Performance Analysis of an Optoelectronic Localization System for Monitoring Brain Lesioning with Proton Beams. Proc. 29th Ann. Int. Conf. .IEEE EMBS, Lyon, France August 23-26, 2007, pp. 4693-8.

Conclusion and Future

- Protons have a long history in radiosurgery but their potential has not been fully exploited
- Physical characteristics of protons favor their use both in radiosurgical applications
- With wider availability of proton gantries at reduced costs more proton radiosurgery centers will be established

Thank you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A SEVENTH-DAY
ADVENTIST INSTITUTION

Typical Variations of Subthalamic Electrode Location Do Not Predict Limb Motor Function Improvement in Parkinson's Disease

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Department of Neurosurgery

University of Minnesota Medical School

Minneapolis, Minnesota

September 7, 2007

Disclosures

- The presenter has no corporate or commercial relationships

- The presenter received no financial support in conjunction with the development of this project

UNIVERSITY OF MINNESOTA

Background

- Stimulation of the subthalamic nucleus (STN) through deep brain stimulation (DBS) is an effective modality for treatment of medically refractory Parkinson's disease (PD)

- In PD patients, STN stimulation has reproducibly demonstrated:
  - Consistent clinical benefit (particularly for motor fluctuations)
  - Reduction of medication requirements postoperatively
  - Improvement of limb function contralateral to the side of electrode placement

- However, there is no consensus regarding how much efficacy is dependent on the anatomical electrode location

Study Objectives

- Very few studies have correlated the accuracy of electrode placement with the clinical outcome of the implanted patients
- No study has correlated the accuracy of electrode placement specifically with <u>quantitative</u> measures of contralateral limb function
- This study was performed to examine this issue

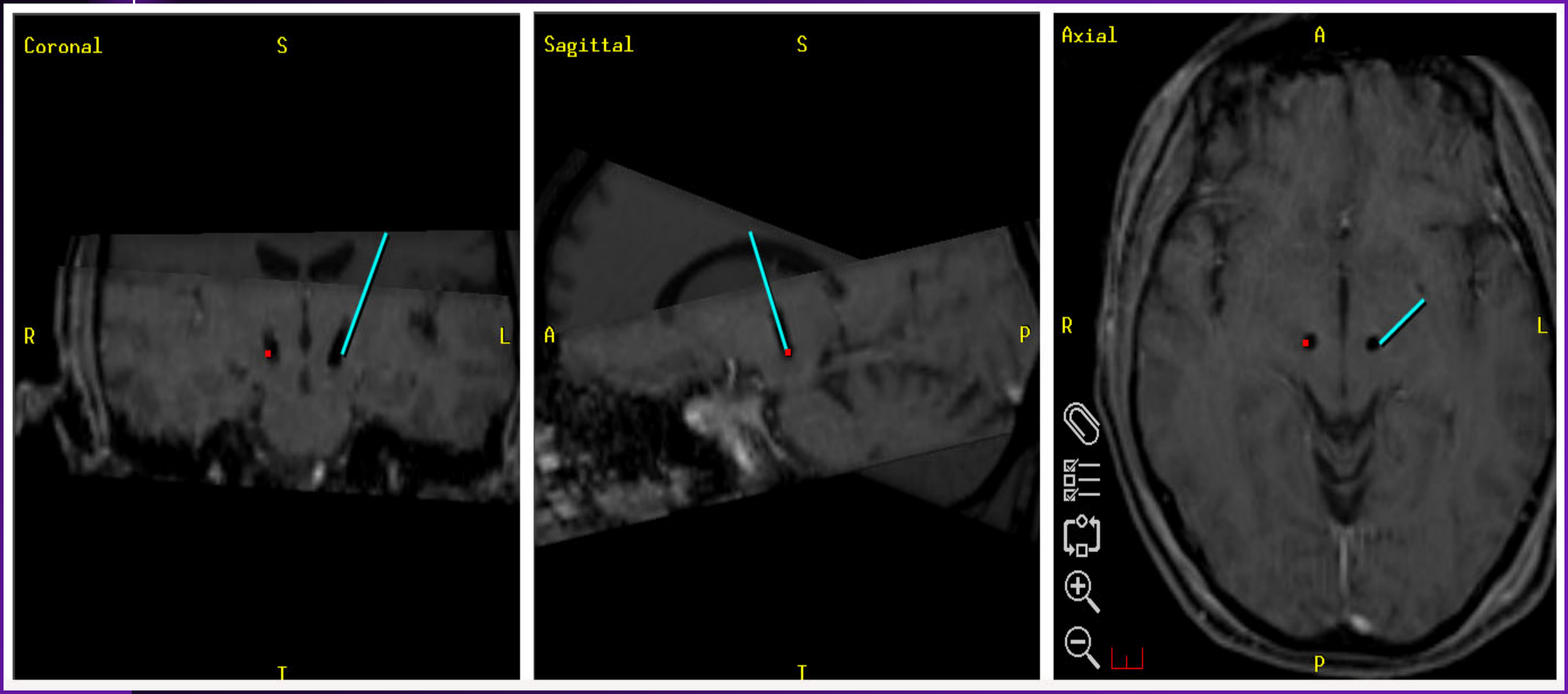
Study Methods

- Performed retrospective analysis of 21 patients who had bilateral STN electrode implantation
- Post-operative MRIs (displaying the electrode) were merged with pre-operative planning MRIs to obtain the actual stereotactic coordinates of the electrode tip

Study Methods (continued)

- These coordinates were then compared with the intended target for the electrode tip by 3 separate analyzers
- Each analyzer was <u>blinded</u> to patient clinical outcome in order to avoid bias in reading of electrode tip coordinates

Coronal, Sagittal, and Axial views (Stealth FrameLink 4.0)
Post-implant MRI has been merged with the pre-operative planning MRI



Red dot = Computer calculated target for the right STN
Blue line = Trajectory for computer calculated target for the left STN

Study Methods (continued)

- Following merging, the variation between intended target and actual electrode tip placement was evaluated
- One year postoperatively, all patients were videotaped
- Videotapes were assessed by a movement disorder neurologist blinded to electrode tip locations

Study Methods (continued)

- From the videotape evaluations, limb function was quantitatively measured
- This measure was tabulated as the sum of the nine limb-related components of the Unified PD Rating Scale (UPDRS)
- Components of limb score:
  - (Hand rest tremor) + (Foot rest tremor) + (Action tremor) + (Upper extremity rigidity) + (Lower extremity rigidity) + (Finger tapping) + (Hand gripping) + (Hand pronation/supination) + (Leg agility)

Study Methods (continued)

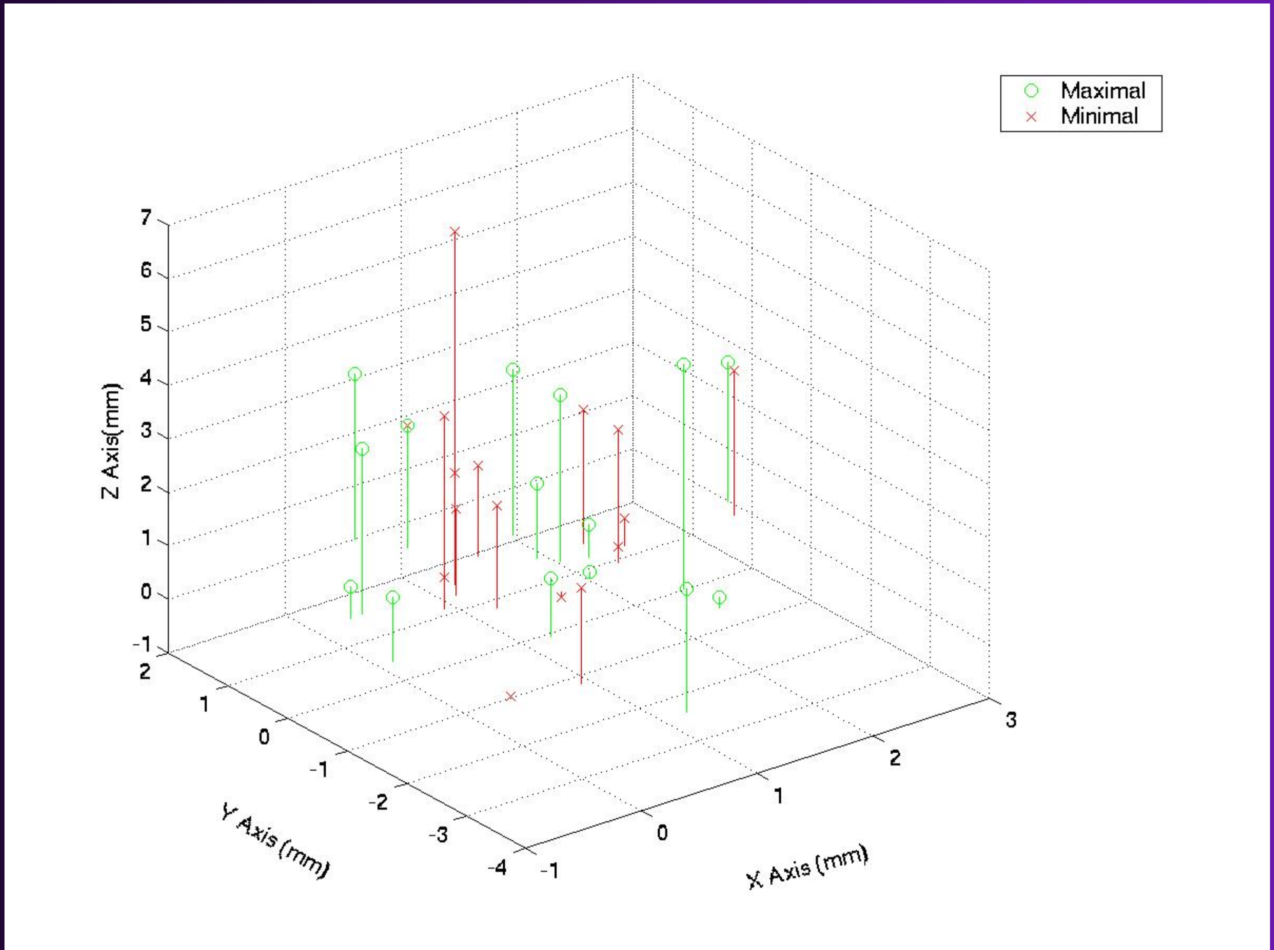
- This tabulation was performed for every electrode, yielding a total of 42 limb scores
- Total score for each electrode = [Score with (off-stim, off-meds)] - [Score with (on-stim, off-meds)]
- Higher score = Greater clinical response to stimulation

Study Methods (continued)

- The electrode tip locations associated with the 15 lowest and 15 highest limb scores were stratified into separate groups
  - Mean limb score of 15 lowest scores = 0.4
  - Mean limb score of 15 highest scores = 15.4
- The groups were then compared in every dimension (lateral-medial; anterior-posterior; superior-inferior) to evaluate for the existence of a distinguishing trend with regard to electrode tip location

Results

- Three-dimensional scatterplot depicting the electrode tip locations associated with the 15 lowest (red) verses 15 highest (green) limb scores



Results (continued)

- There was no significant ($P < 0.05$) difference in electrode tip location between the two groups in any dimension (two-tailed t-test)
  - Lateral-medial [X]; $P = 0.98$
  - Anterior-posterior [Y]; $P = 0.95$
  - Superior inferior [Z]; $P = 0.89$
  - Three-dimensional [square root of $(X^2 + Y^2 + Z^2)$]; $P = 0.76$

- This finding was highly correlated between the three analyzers

- The range of difference in tip location (X-axis = 7.6 mm; Y-axis = 6.1 mm) and limb scores (-2.5 to 22.5) was significant

Conclusions

- Postoperative MRI-determined electrode position does not predict the degree of contralateral limb motor parkinsonism improvement

- Other factors may have a greater bearing on limb motor response, such as:
  - Disease duration
  - Biologic variability between patients
  - Variable current spread to surrounding structures

Conclusions

- Optimal clinical efficacy allows a range of tolerance for STN lead location variability

- The results of this study lend support to the conclusion of our previous report:
  - Clinical efficacy is equivalent with DBS electrode placement anywhere within a 6 mm diameter tissue cylinder centered at the indirectly defined (relative to the ICM on MRI) STN center
    - McClelland et al., *Neurosurgical Focus* 19(5): E12, 2005

- Consequently, anatomic targeting alone may provide the same clinical efficacy as that achieved by "fine-tuning" DBS placement with microelectrode recording to a specific target within the STN

Acknowledgements (Columbia University PD Team)

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- Guy M. McKhann II MD
- Qiping Yu PhD

A Multi-Center Consortium Study of Competing Platforms for Stereotactic Brain Irradiation

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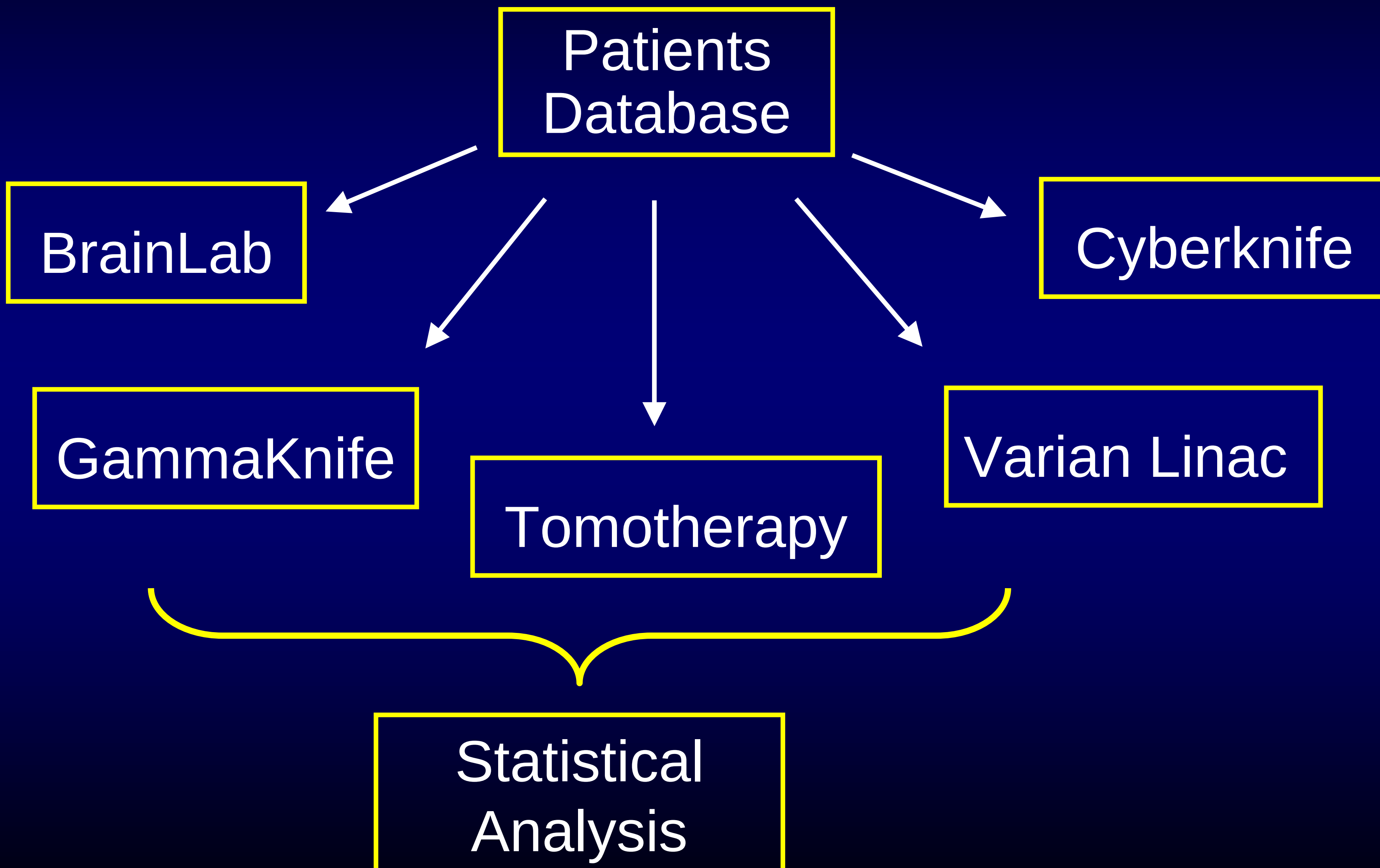
City of Hope National Medical Center
Duarte, CA

Purpose

To evaluate quantitatively the dosimetric advantages / disadvantages of different platforms for stereotactic radiosurgery by comparing treatment plans generated on GammaKnife, BrainLab Novalis, Helical Tomotherapy, Cyberknife and Varian Linac SAS IMRT.

Study Design



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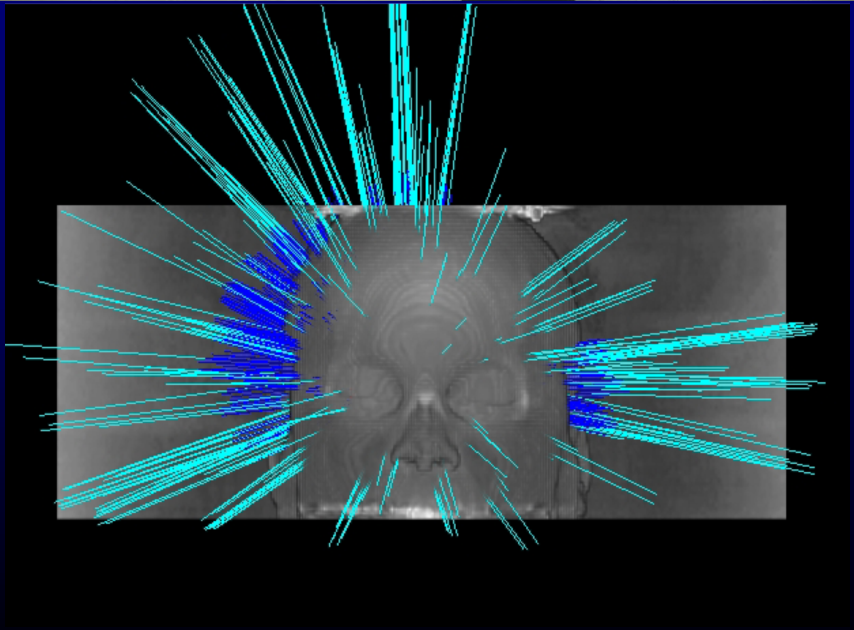
ShangHai Tumor Hospital

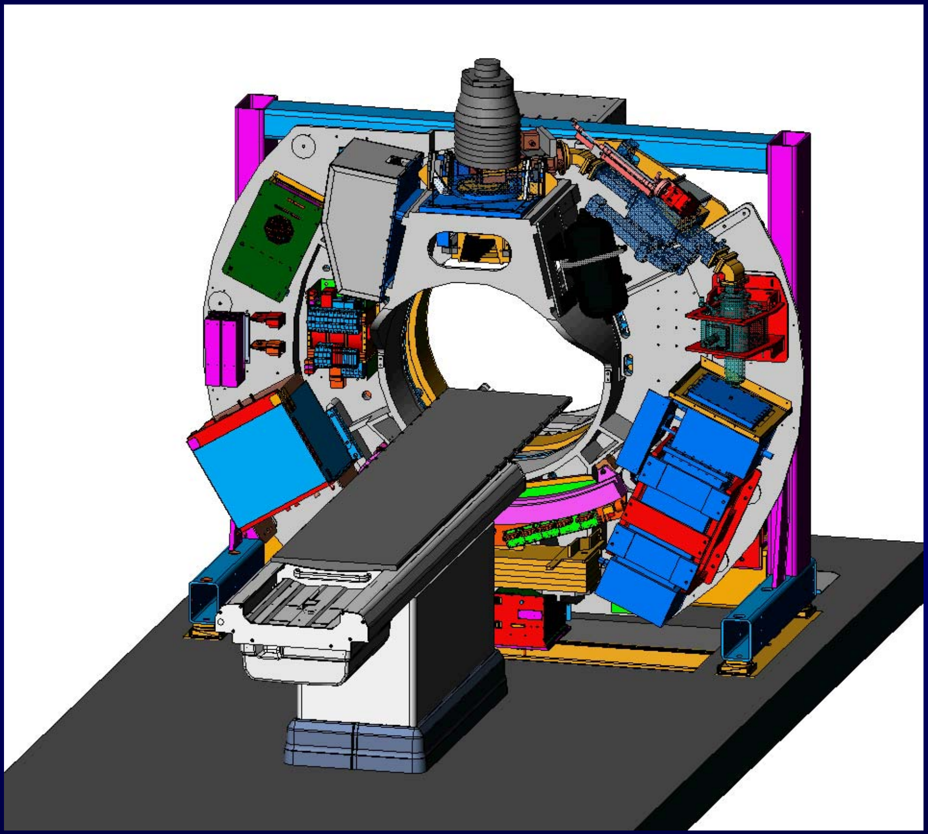
HongHua Lu, M.D.



CyberKnife

- 6MV photon Linac on robotic arm
- 12 Collimators: 5mm-60mm
- Max number of beams: 1200, 1700
- Real time tracking through orthogonal x-ray

Helical Tomotherapy



- 6 MV photon beam
- CT detector system
- Rotating gantry
- Slice thickness 0.5 - 5 cm
- Min. beamlet size 5 x 6.25 mm
- Fan beam width 40 cm
- Couch movement up to 160 cm
- Dynamic Arc IMRT with image guidance

Evaluation Criteria

- Conformity Index:

$$CI = \frac{V_{PTV} \times V_{tissue}}{TV_{PV}^2}$$

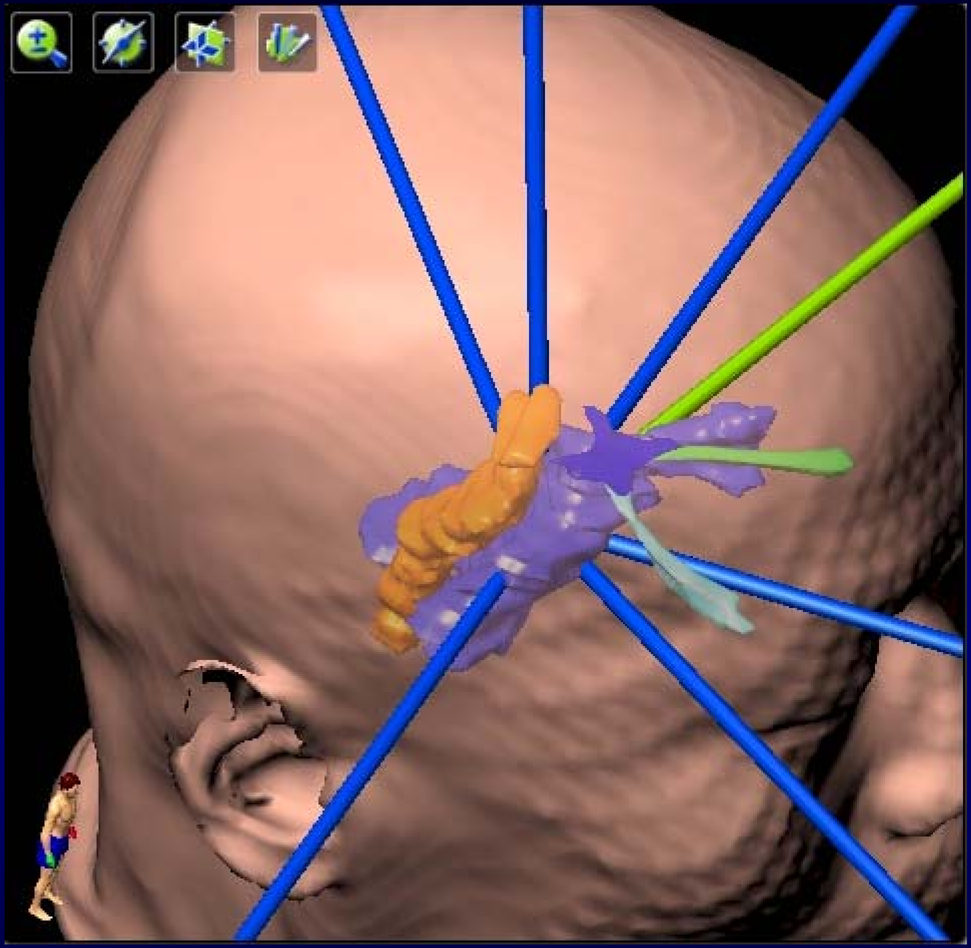
- Homogeneity Index:

$$HI = \frac{D_{\max}}{D_{Rx}}$$

- Gradient Score Index (GSI):

$$GSI = 100 - 100 \times [(R_{Eff,50\% Rx} - R_{Eff,Rx}) - 0.3\mathrm{cm}]$$

- Critical Organ Integral dose

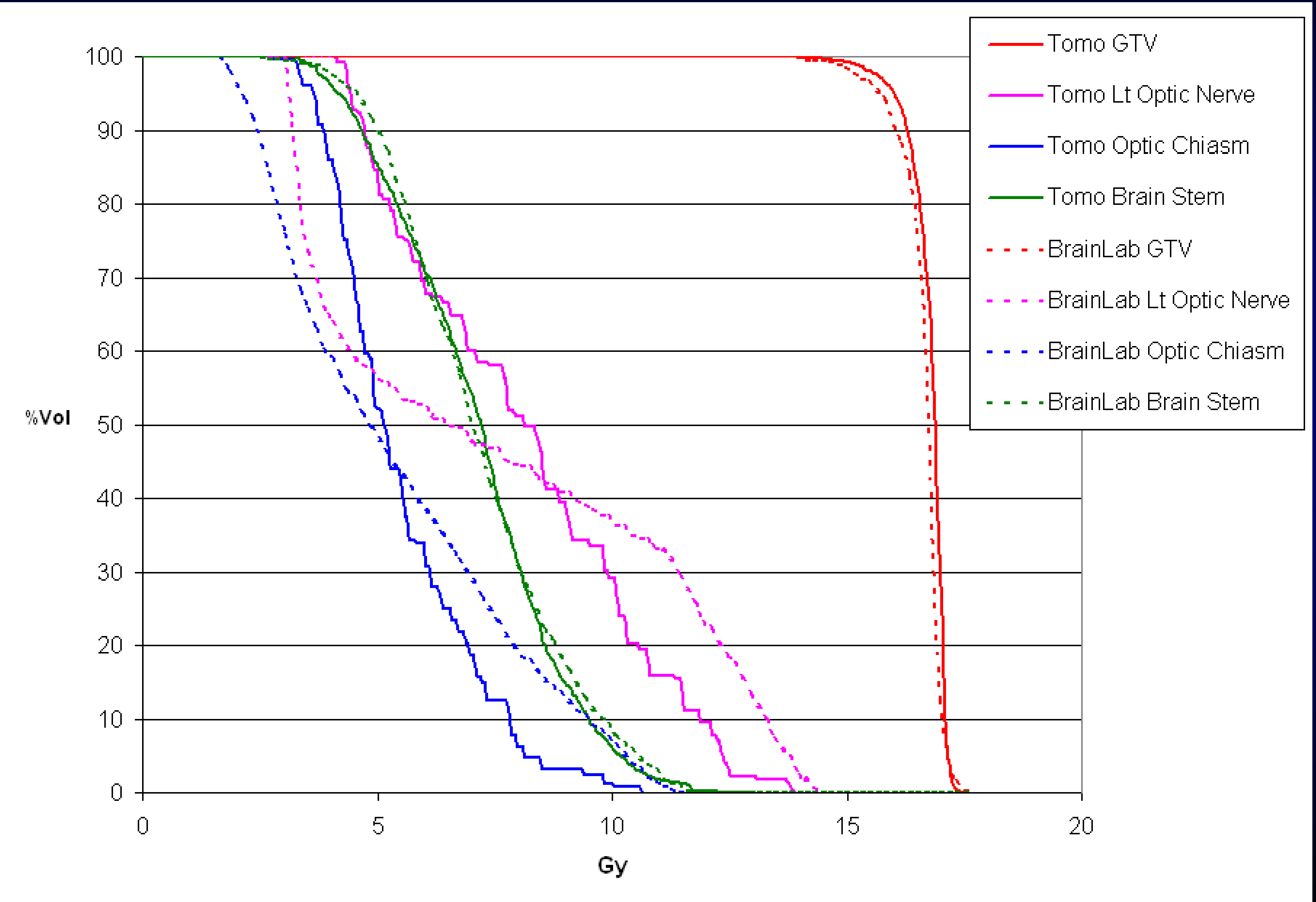


- Case#1: Arteriovenous malformation (AVM)
- Tumor Vol: 29cc
- Wrapping around brainstem, optic chiasm, left optic nerve
- 16Gy single shot

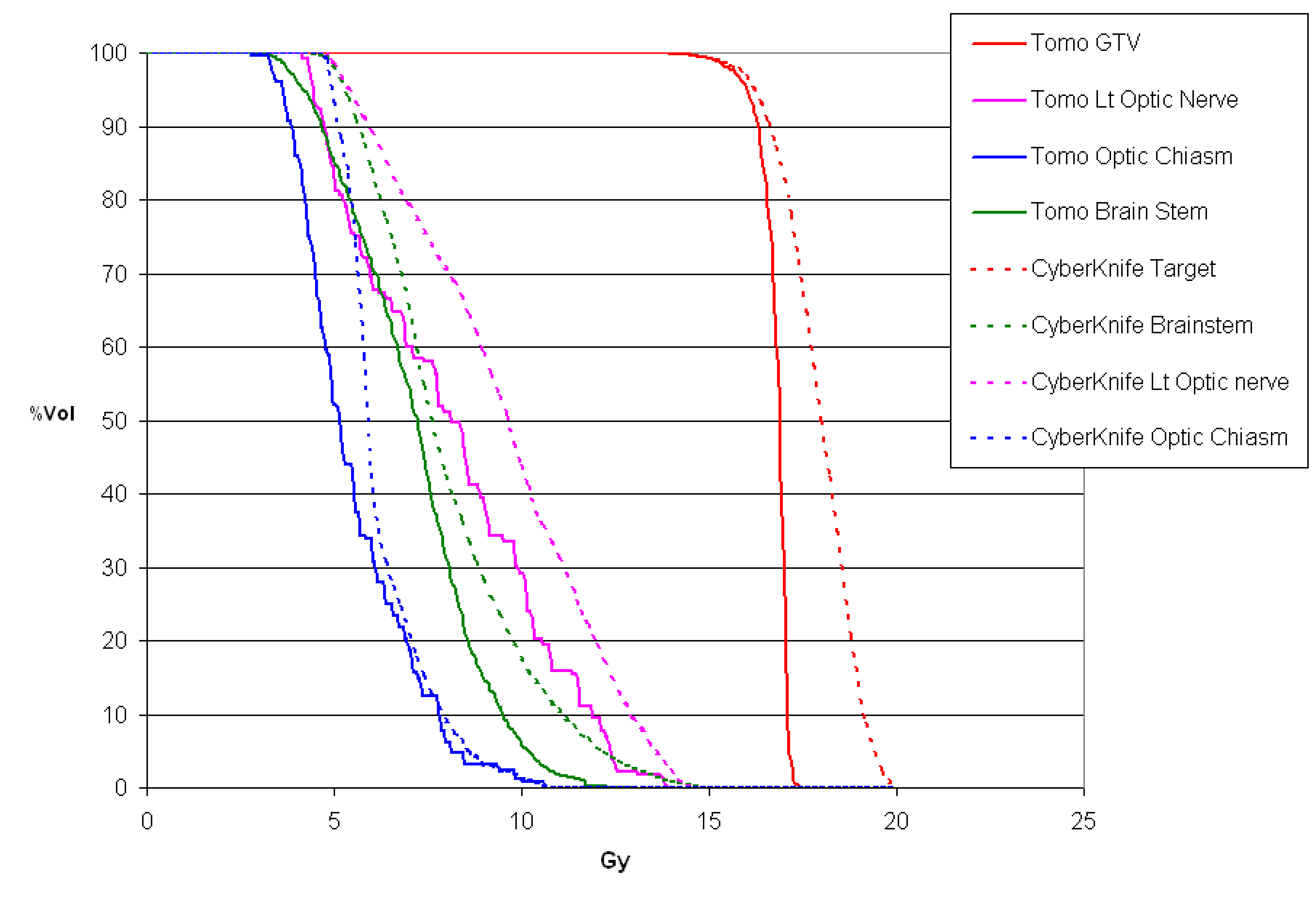
Case #1

- BrainLab plan: 7 non-coplanar field IMRT with 3mm miniMLC
- CyberKnife: 10mm cone, 350 beams
- Helical Tomotherapy: co-planar 360 dynamic arc IMRT
- Varian Linac: 7 non-coplanar step and shoot IMRT fields with 5mm MLC

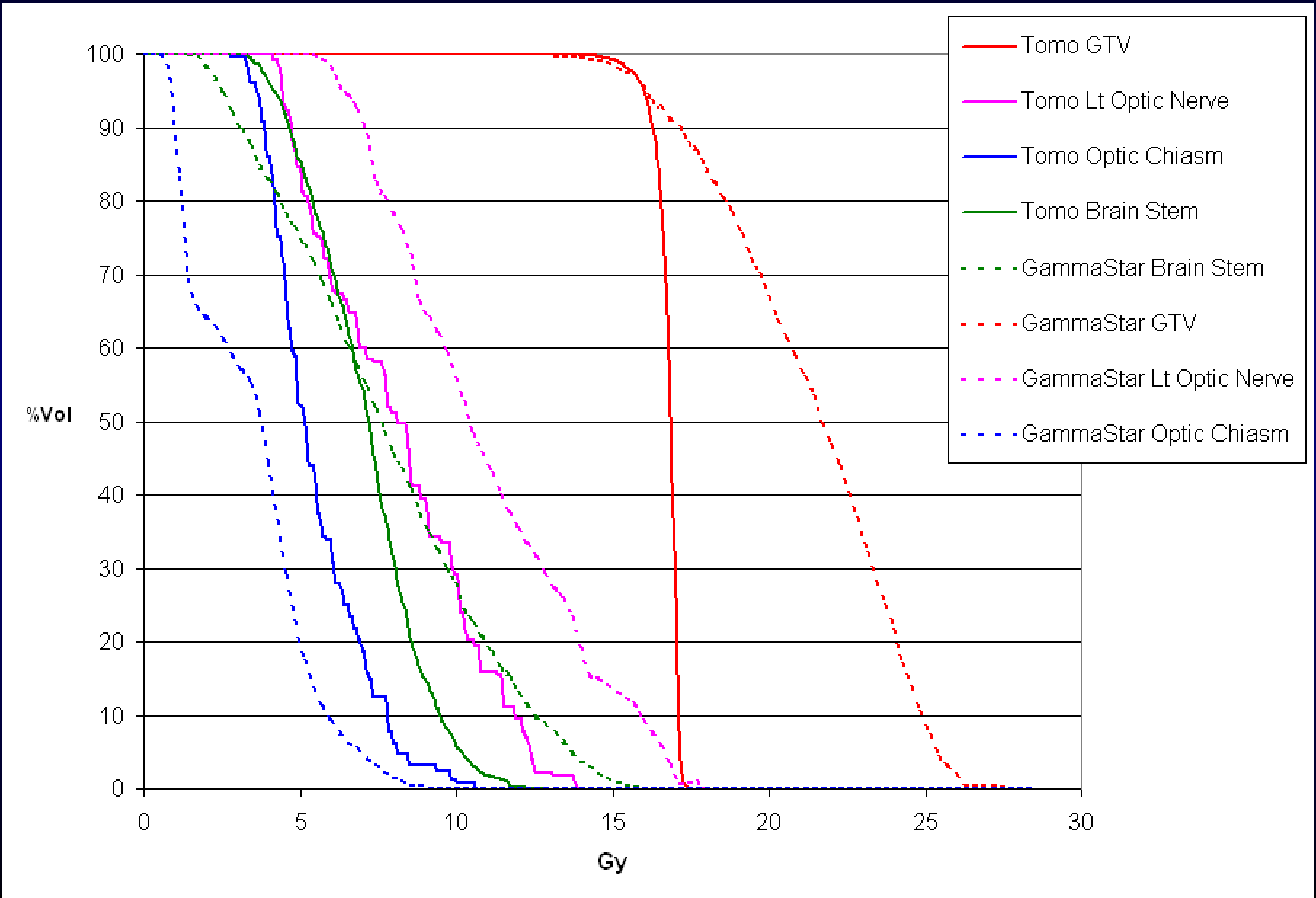
Helical TomoTherapy vs BrainLab



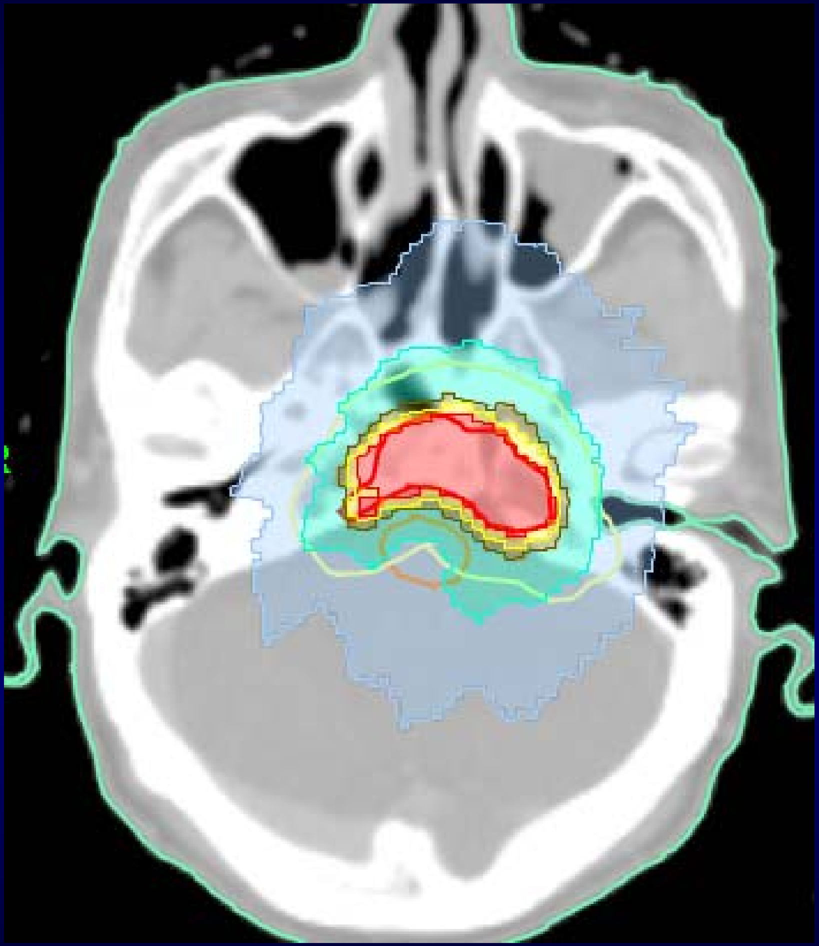
TomoTherapy vs CyberKnife



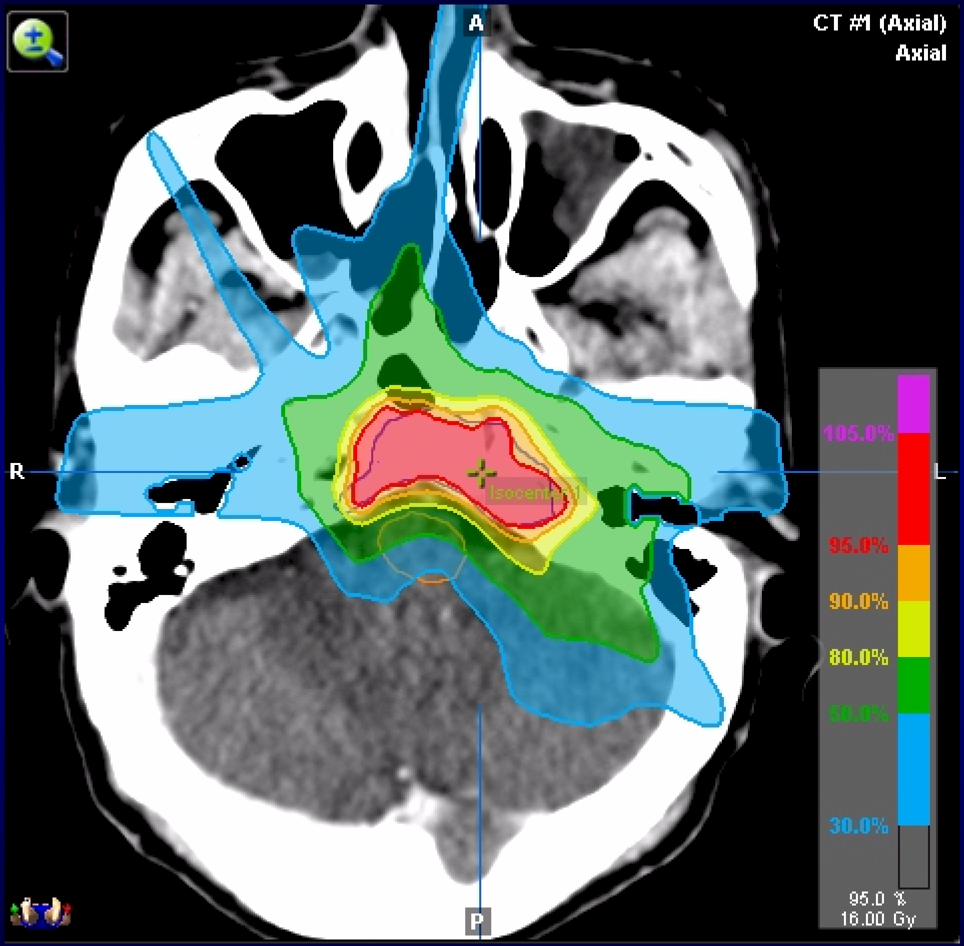
TomoTherapy vs GammaStar



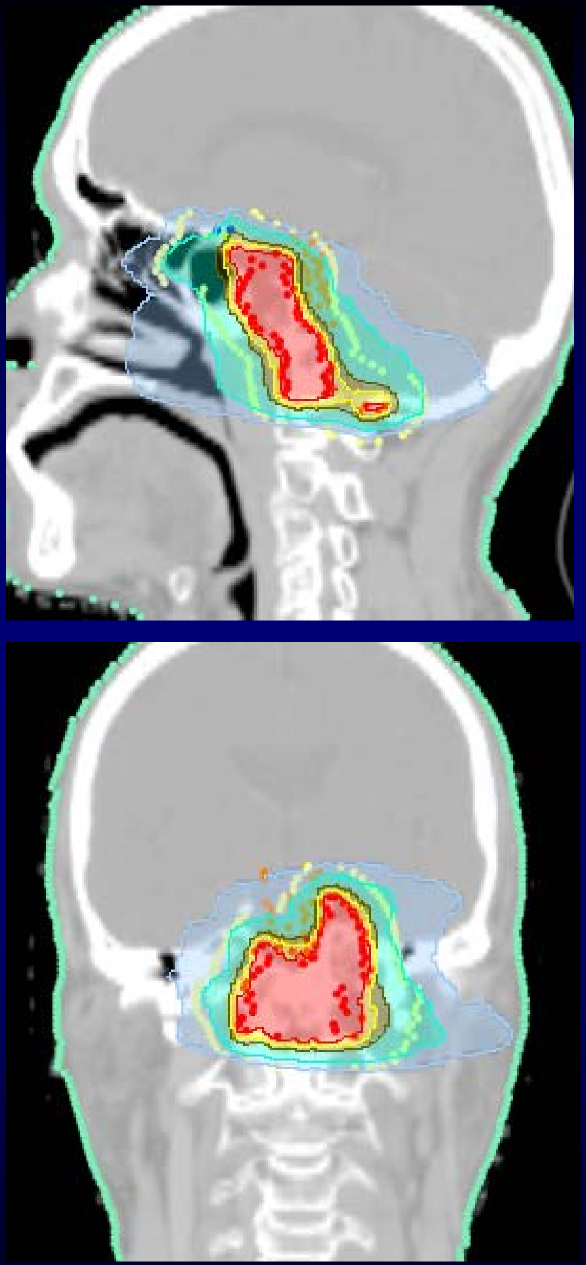
Helical TomoTherapy vs BrainLab



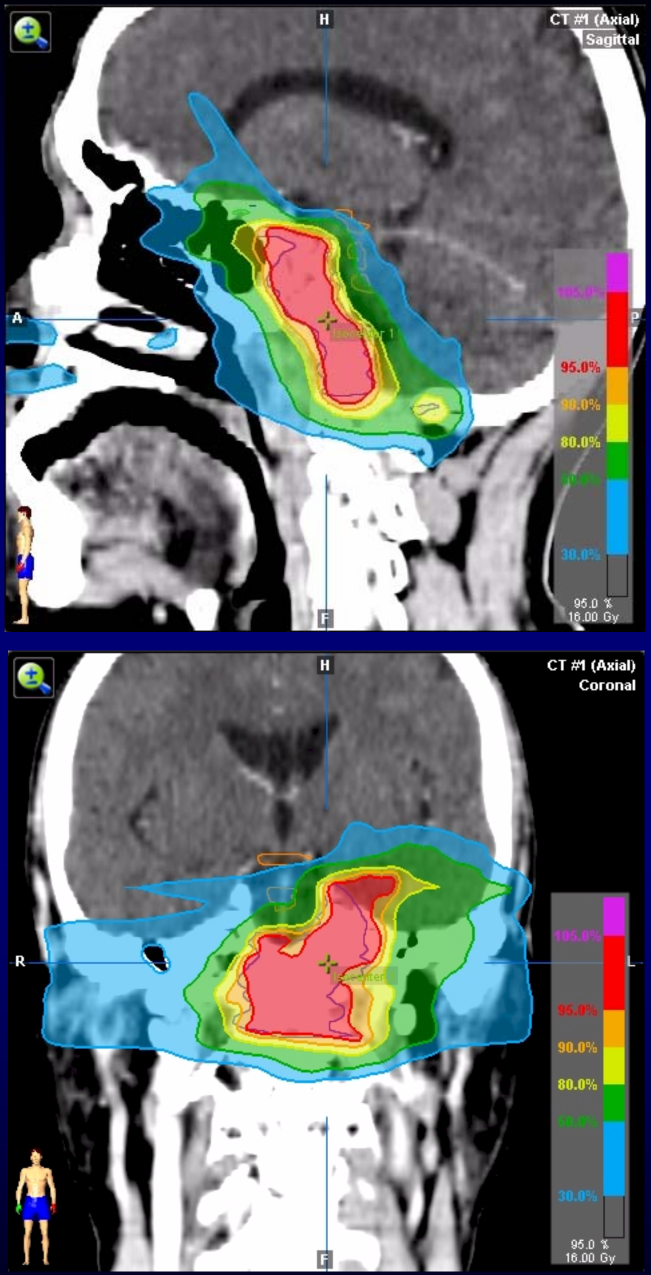
Tomo



BrainLab

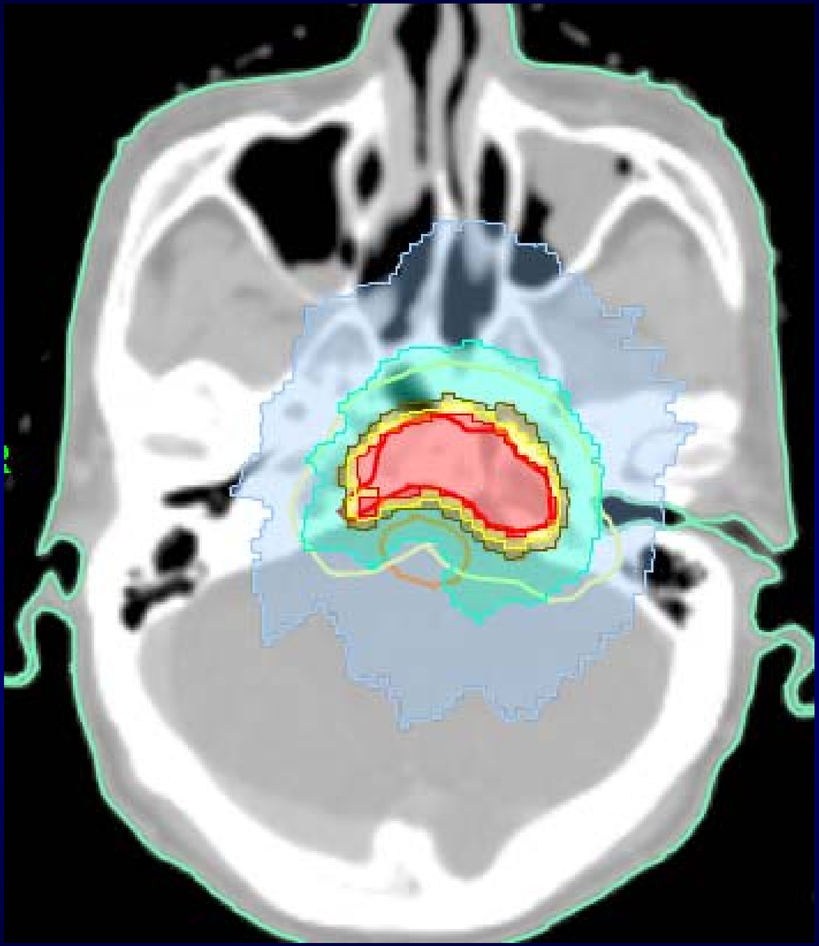


Tomo

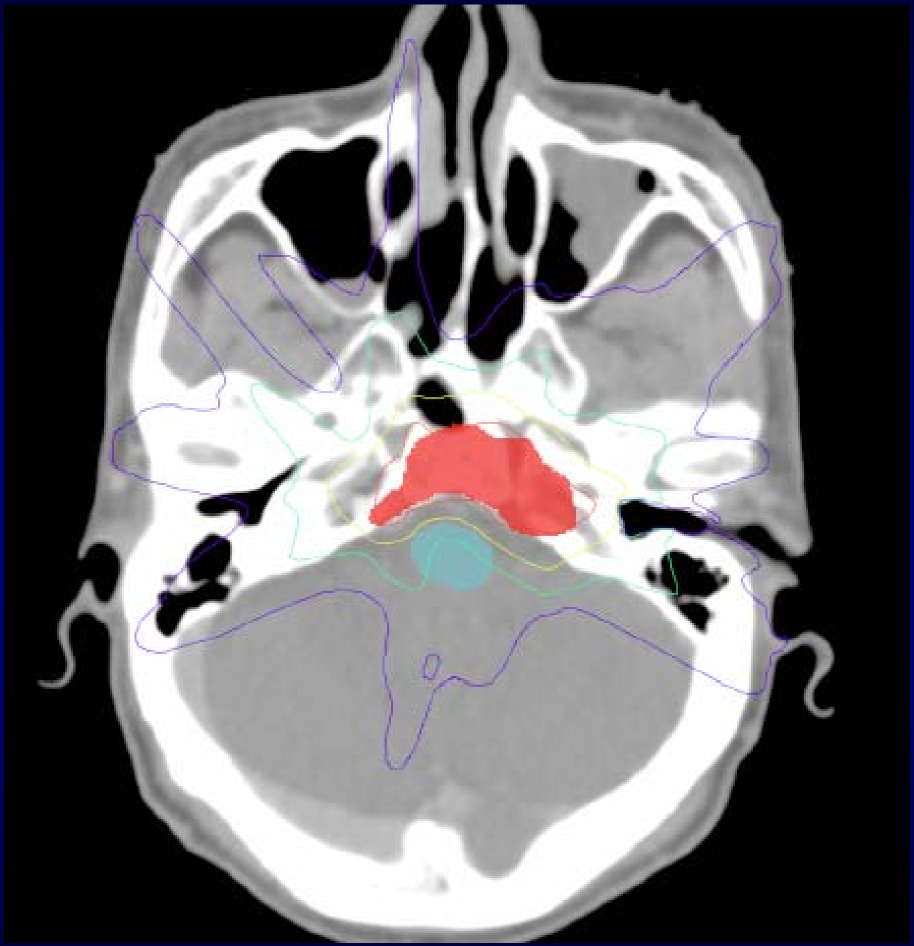


BrainLab

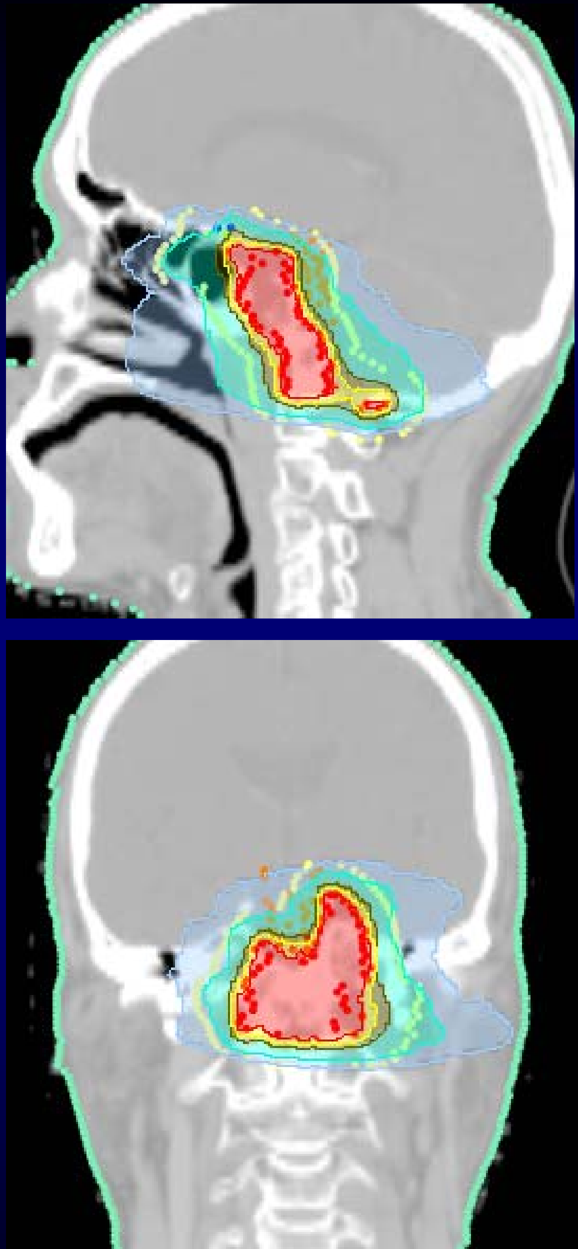
Helical TomoTherapy vs Varian



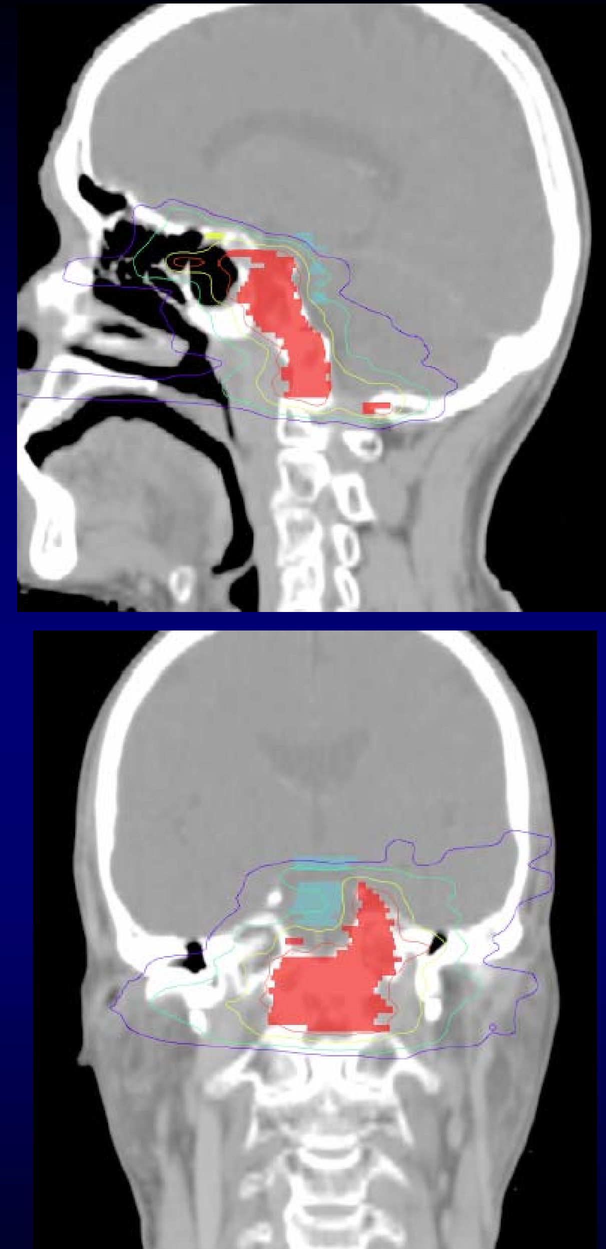
Tomo



Varian 21EX



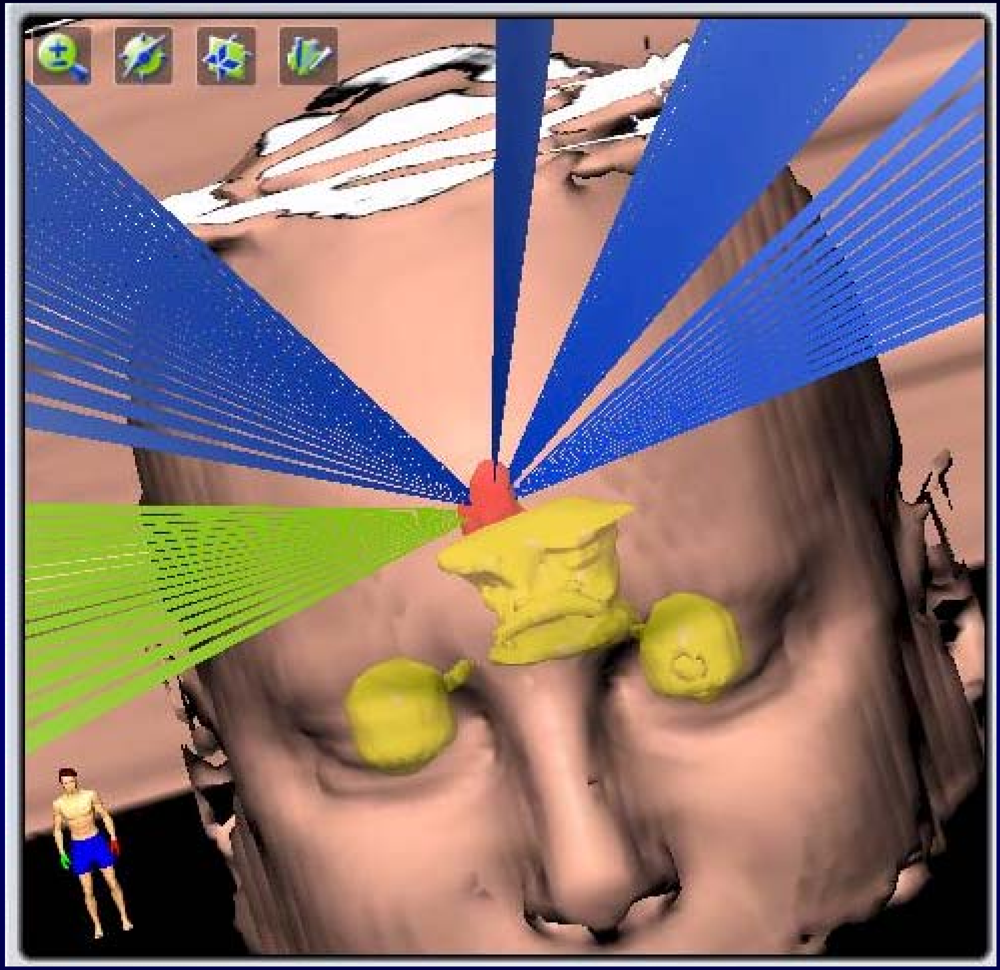
Tomo



Varian 21EX

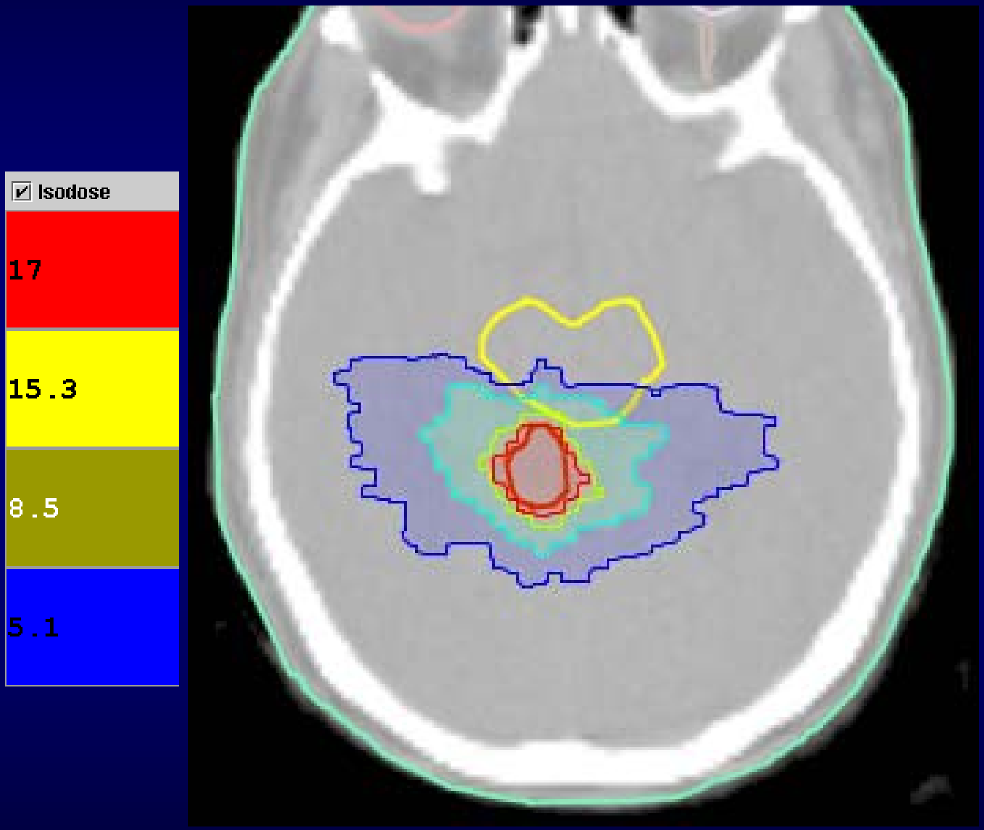
Comparison Index
Case #1

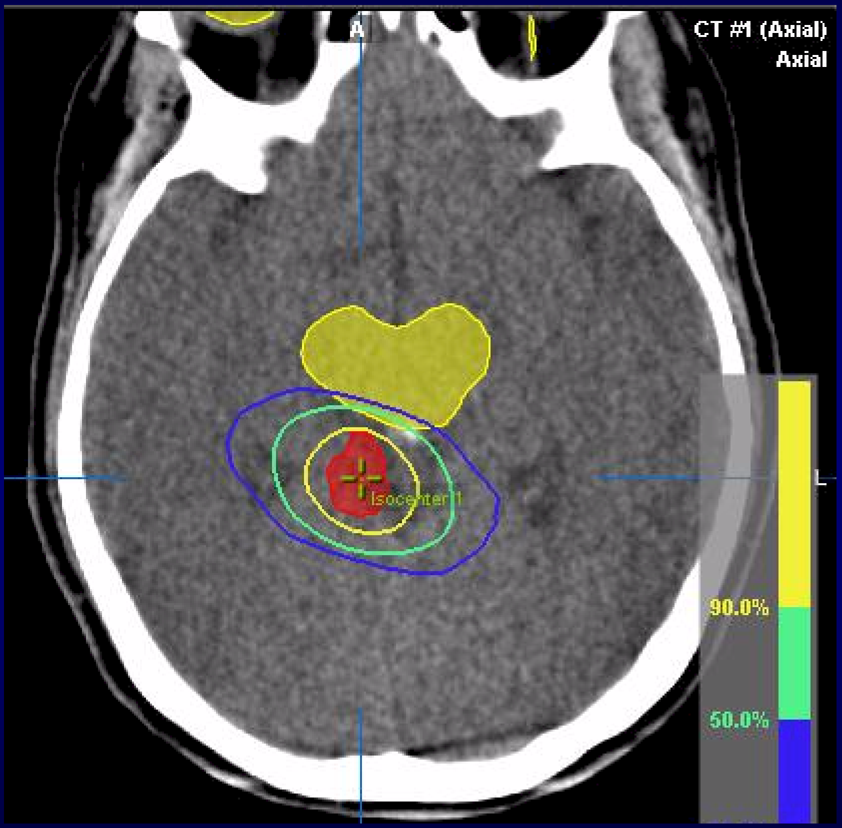
	BrainLab	Tomo	Varian/Corvus	CyberKnife	GammaStar
Conformity Index					
CI	1.82	1.35	1.55	1.38	2.18
Homogeneity Index					
HI	1.09	1.09	1.21	1.25	1.79
Gradient Score Index					
Dose gradient %/mm	2.96	3.59	3.20	3.60	4.54
GSI	-38.92	-9.08	-26.46	-8.75	19.75
Normal Organ Integral Dose (Gy*g)					
Brain Stem	74.18	73.73	75.92	8.35	80.24
Lt Optic Nerve	3.61	4.54	4.98	5.34	6.11
Optic Chiasm	2.71	3.42	2.70	3.89	2.11
Rt Optic Nerve		3.37	2.88	3.65	1.12



- Case#2: Metastatic Adenocarcinoma
- GTV: 0.8cc; CTV: 1.6cc
- Next to brainstem
- 17Gy single shot
- BrainLab plan: 5 non-co-planar conformal arcs

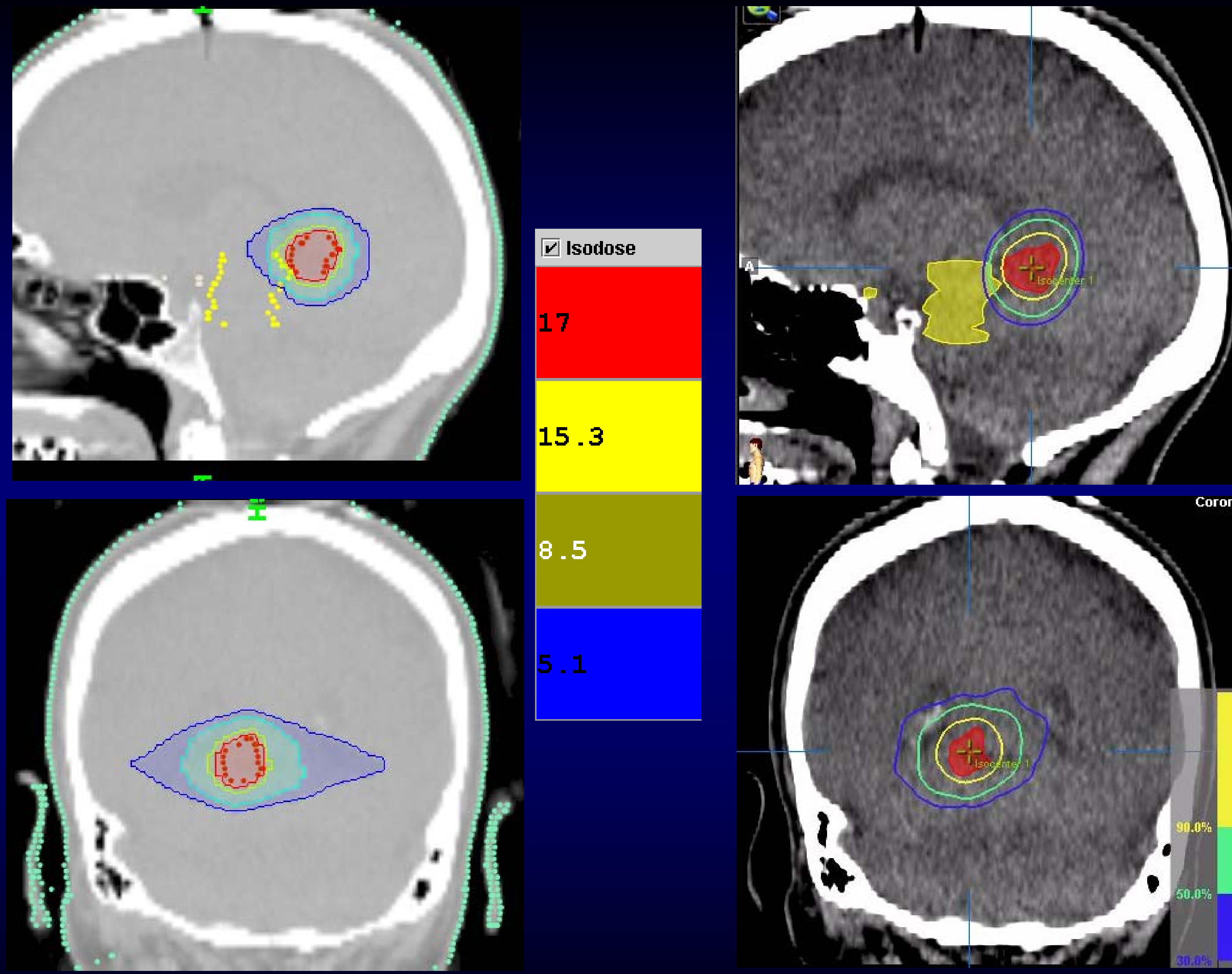
Helical TomoTherapy vs BrainLab Case #2





Tomo

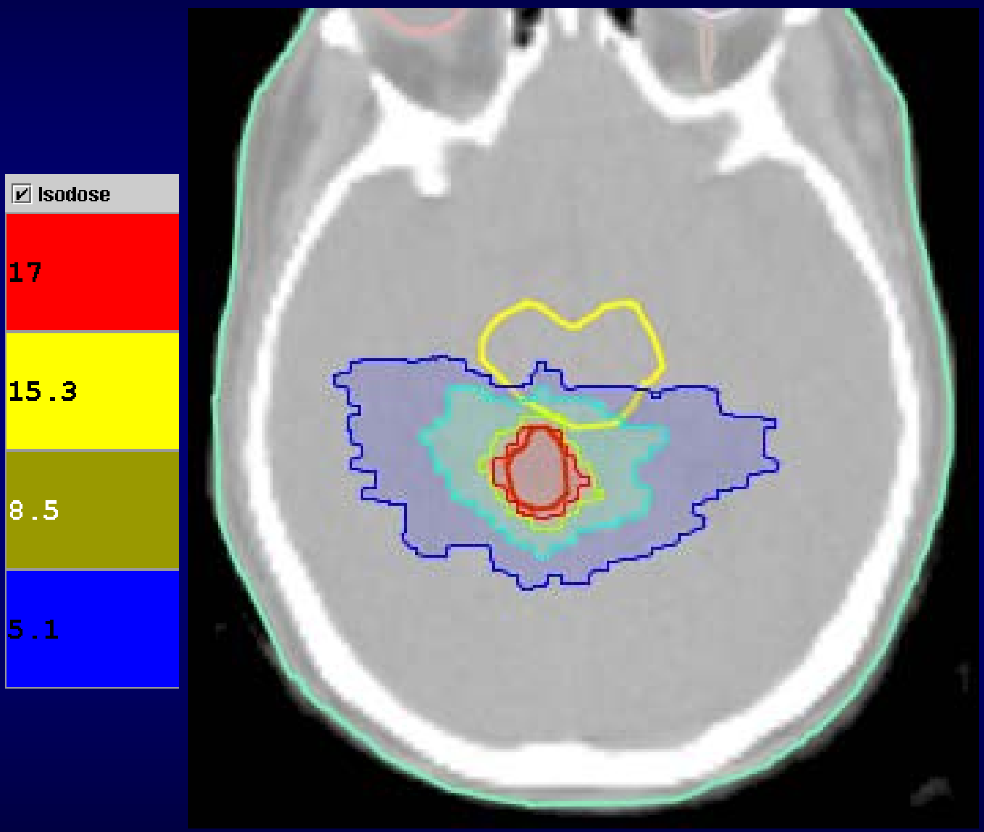
BrainLab

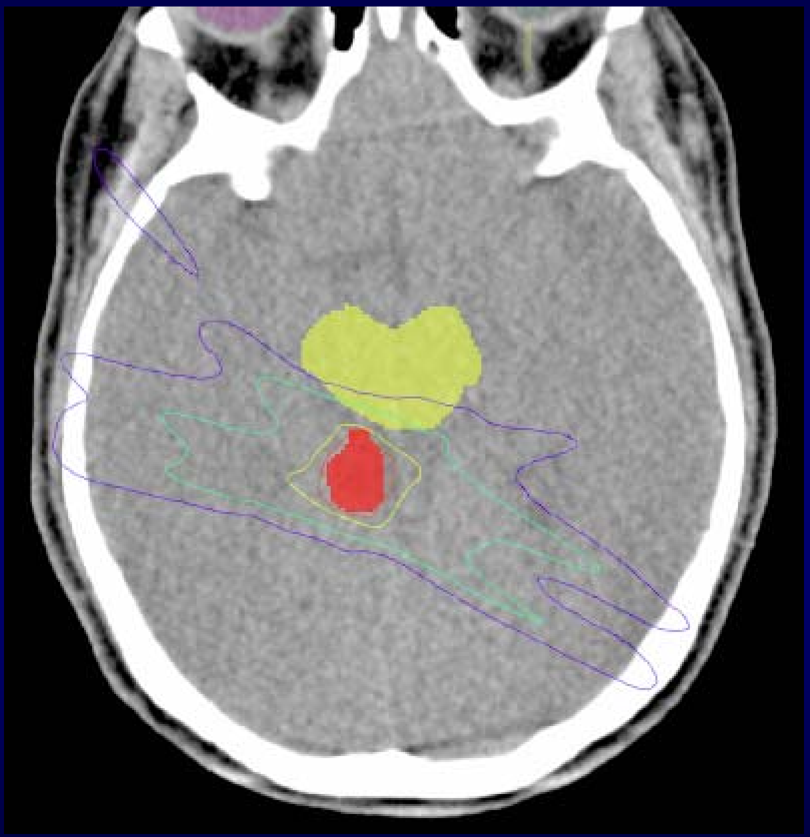


Tomo

BrainLab

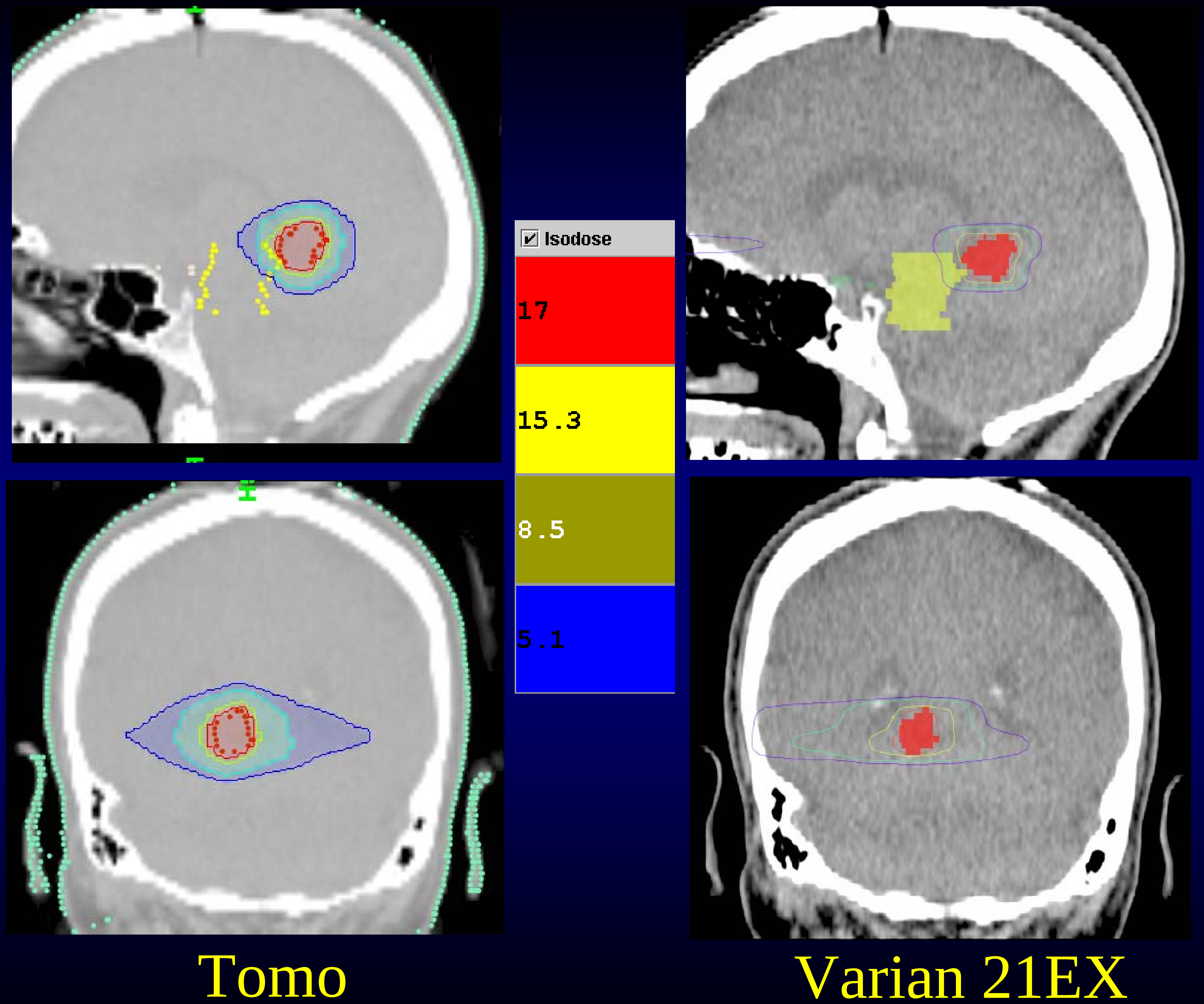
Helical TomoTherapy vs Varian Case #2

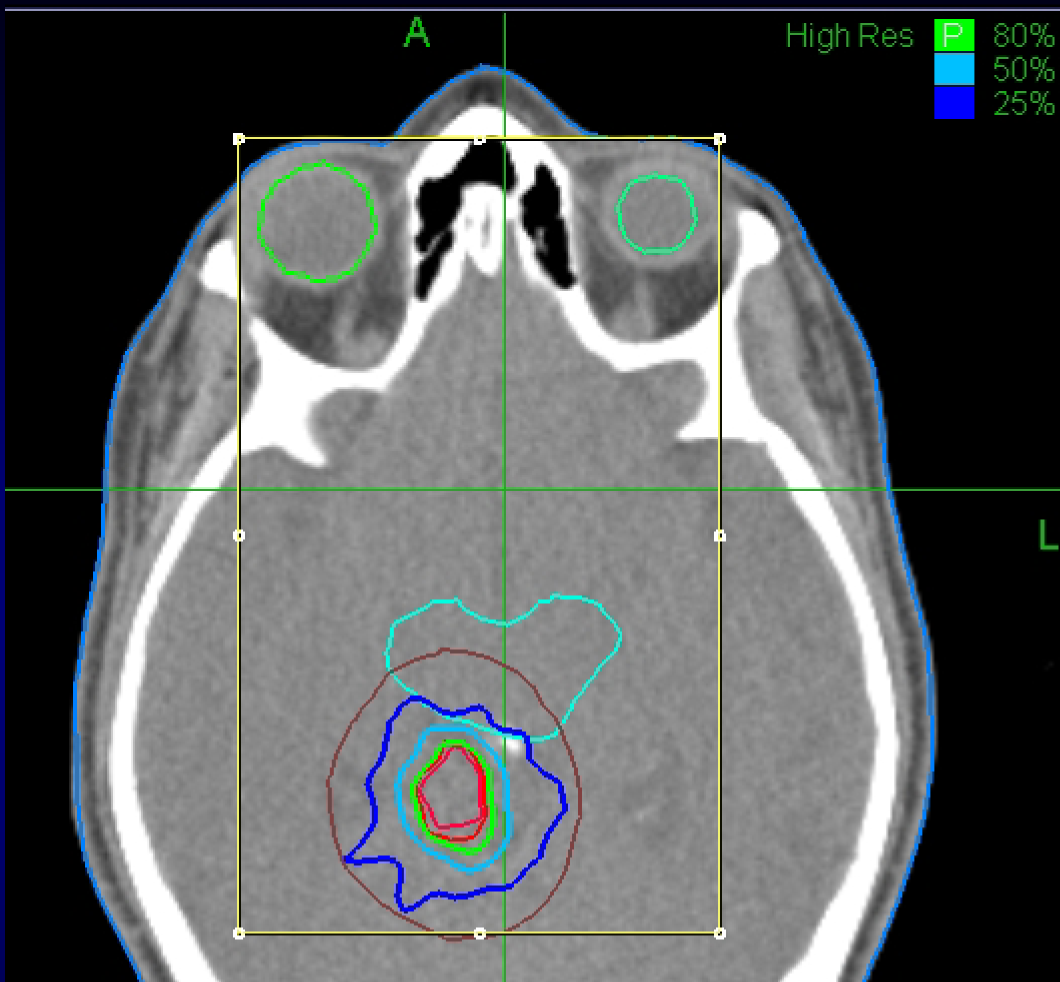




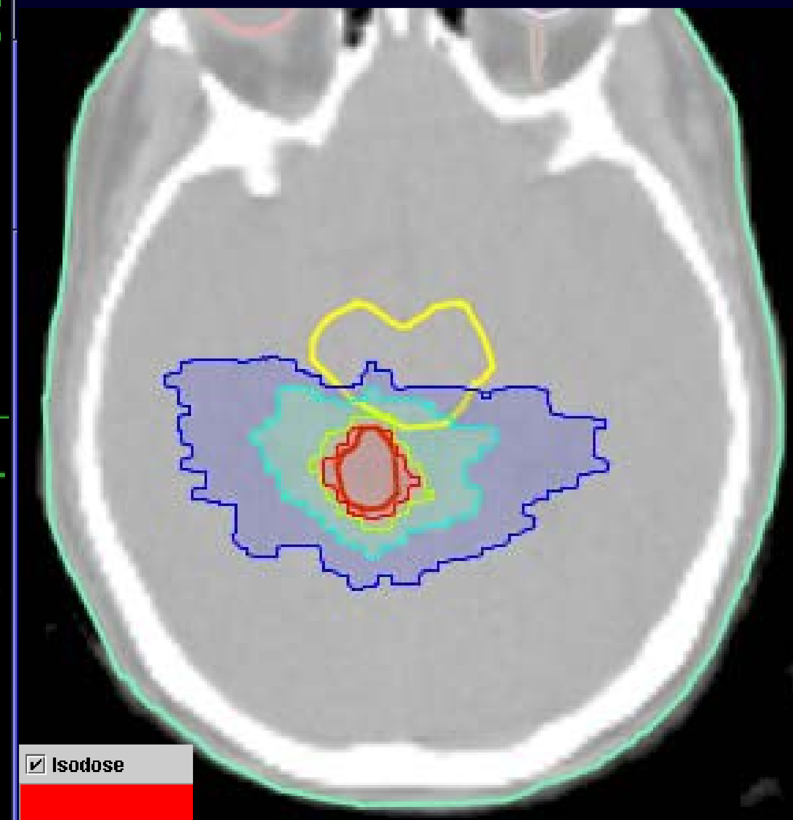
Tomo

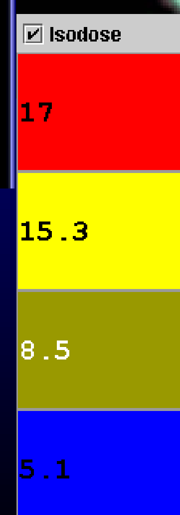
Varian 21EX


Isodose
17
15.3
8.5
5.1
Tomo
Varian 21EX



CyberKnife





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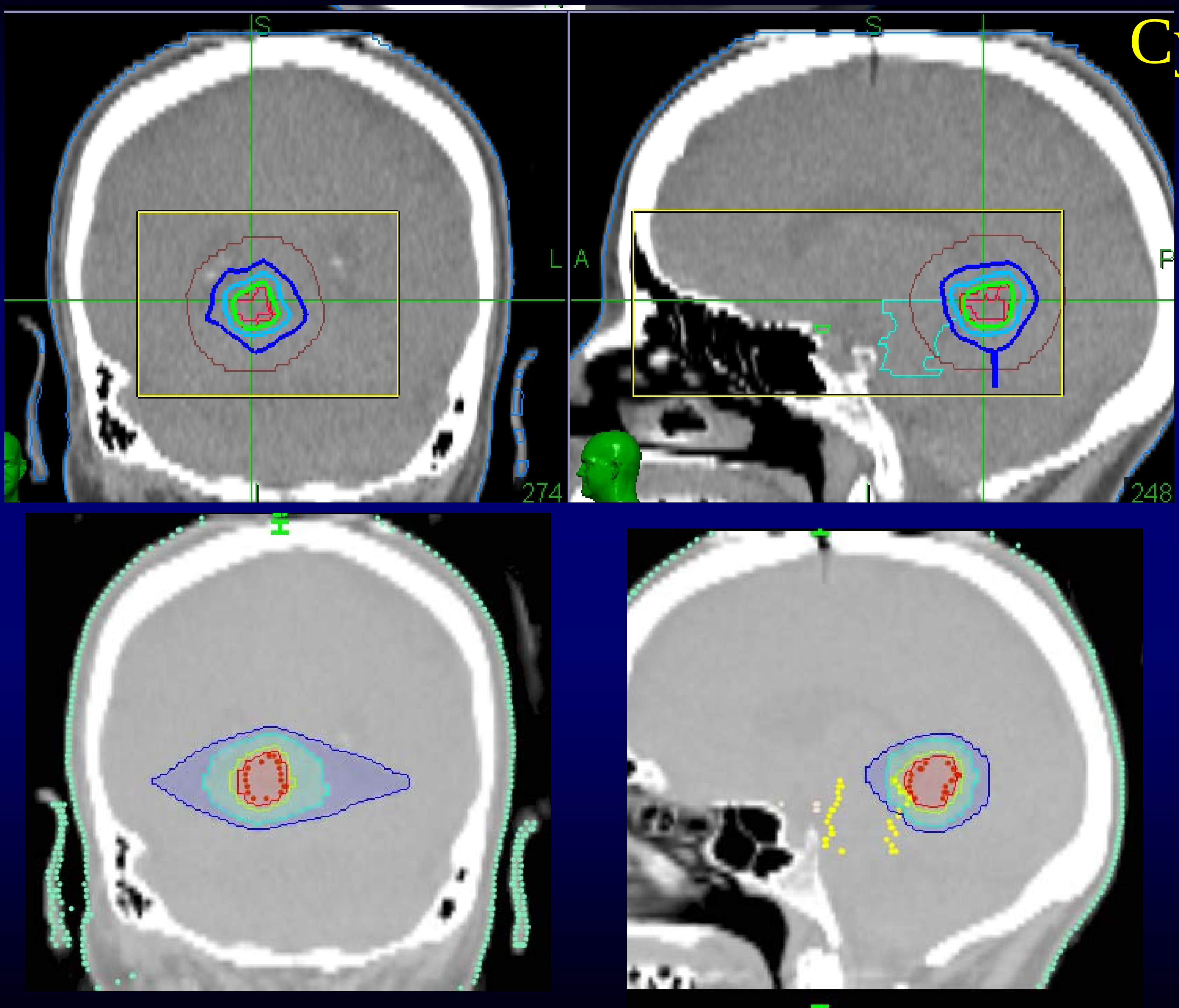
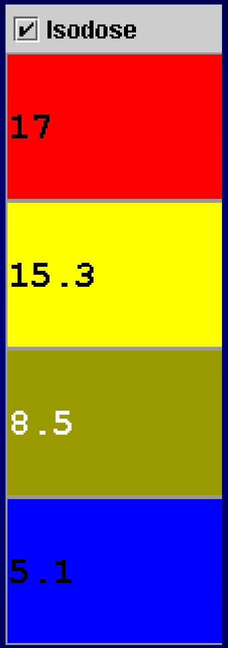
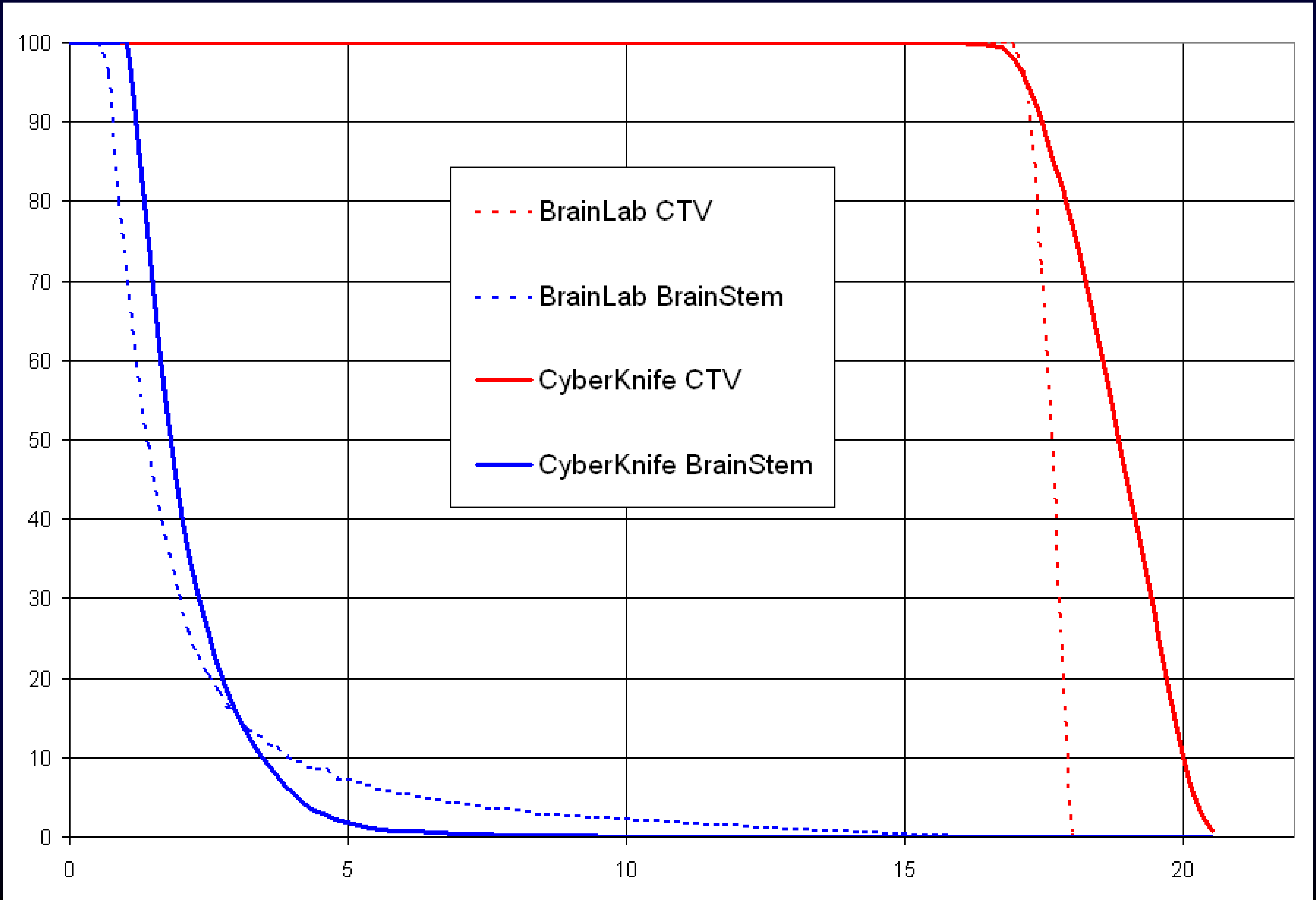


CyberKnife

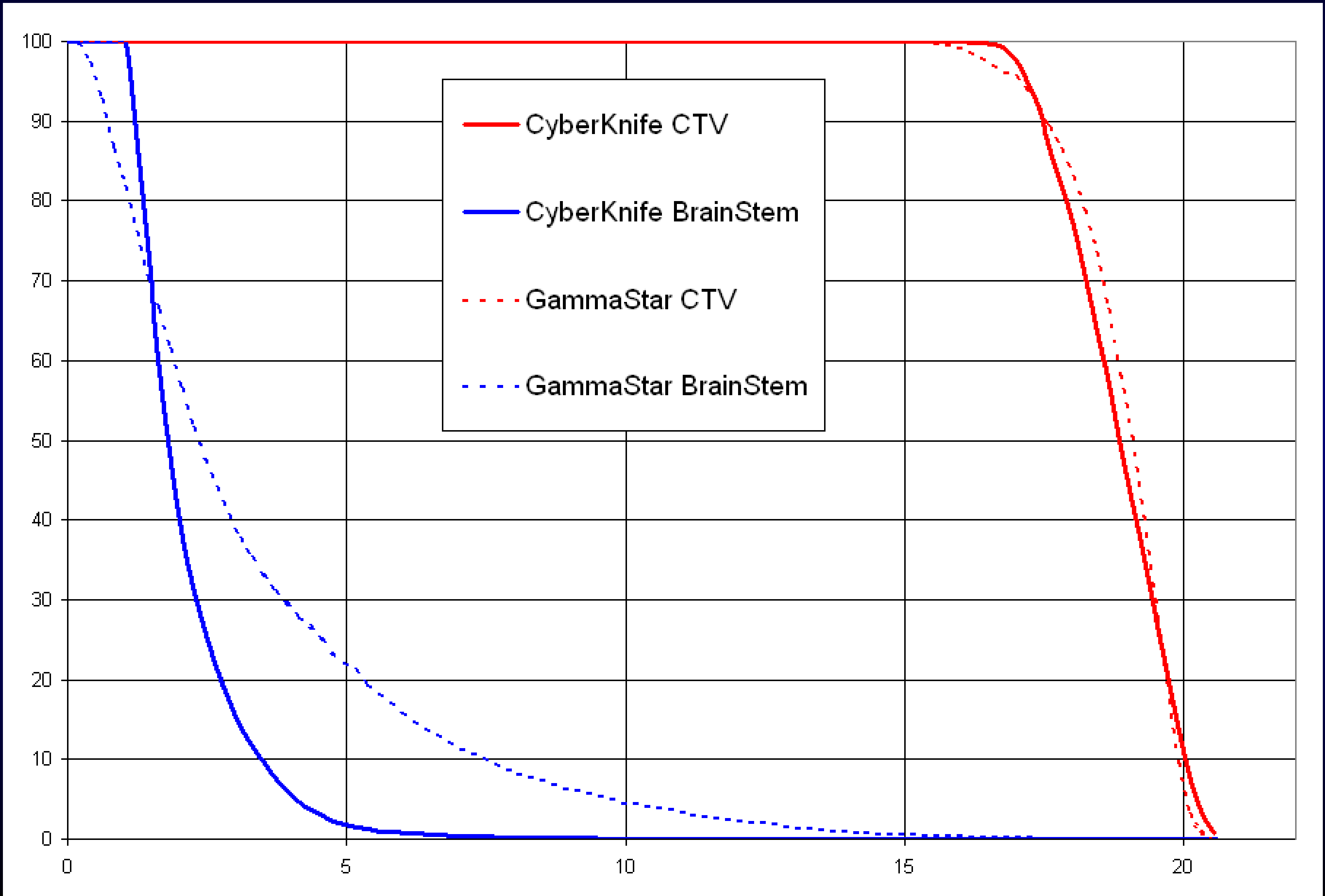


Tomo

BrainLab vs CyberKnife: Case #2



CyberKnife vs GammaStar: Case #2



Comparison Index
Case #2

	BrainLab	TomoTherapy	Varian/Corvus	CyberKnife	GammaStar
Conformity Index					
CI	2.30	1.82	1.58	1.19	1.83
Homogeneity Index					
HI	1.07	1.33	1.14	1.22	1.22
Gradient Score Index					
Dose gradient %/mm	7.27	9.35	5.18	13.19	9.01
GSI	61.25	76.51	33.40	92.11	74.49
Normal Organ Integral Dose (Gy*g)					
Brain Stem	28.24	31.42	29.11	31.18	45.16

Multi-Parametric Imaging in Brain Metastases: Measuring Cognitive and Overall Response to Whole Brain Radiation

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Vanderbilt University Medical Center

Nashville, Tennessee, USA

NIH/NCI 2R25 CA092043-06 NIH/NCRR M01 RR 00095

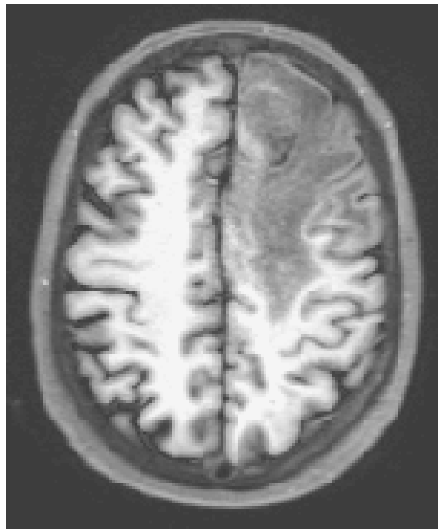
Brain Metastases

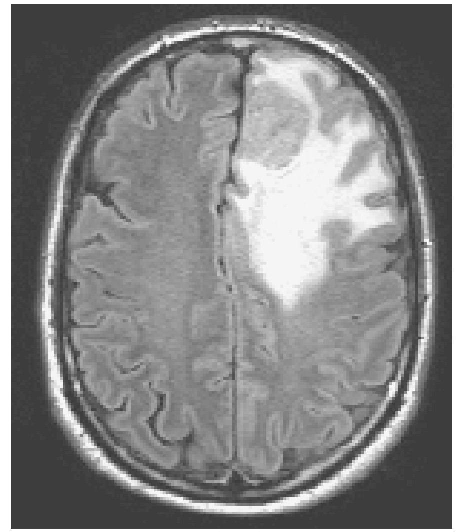
- 10-30% of cancer patients
- Tumor Progression vs. Whole brain radiation treatment
- Treatment
  - Whole Brain External Beam Radiation Therapy
    - 30 Gy in 15 fx
  - Chemotherapy
  - Steroids

QuickTime™ and a
decompressor
are needed to see this picture.

Pre-Therapy Multi-Modal Imaging

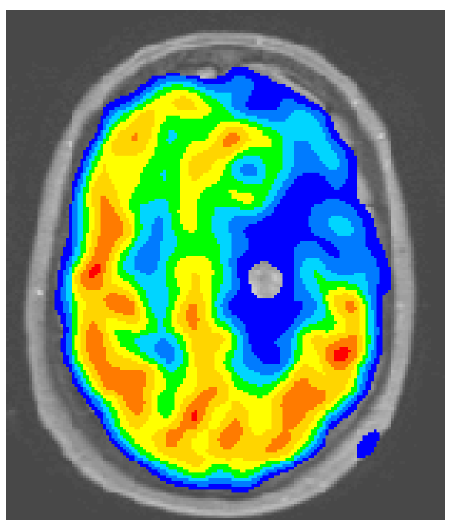
T1
Abnormal extent

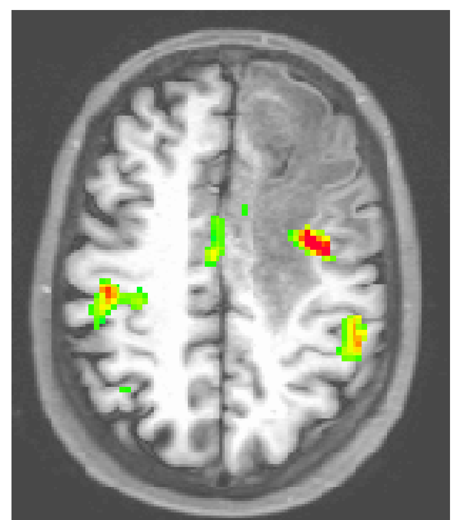




T2 FLAIR
Tumor and Edema

FDG-PET
Glucose uptake





fMRI
Simon
BOLD response to attentional conflict

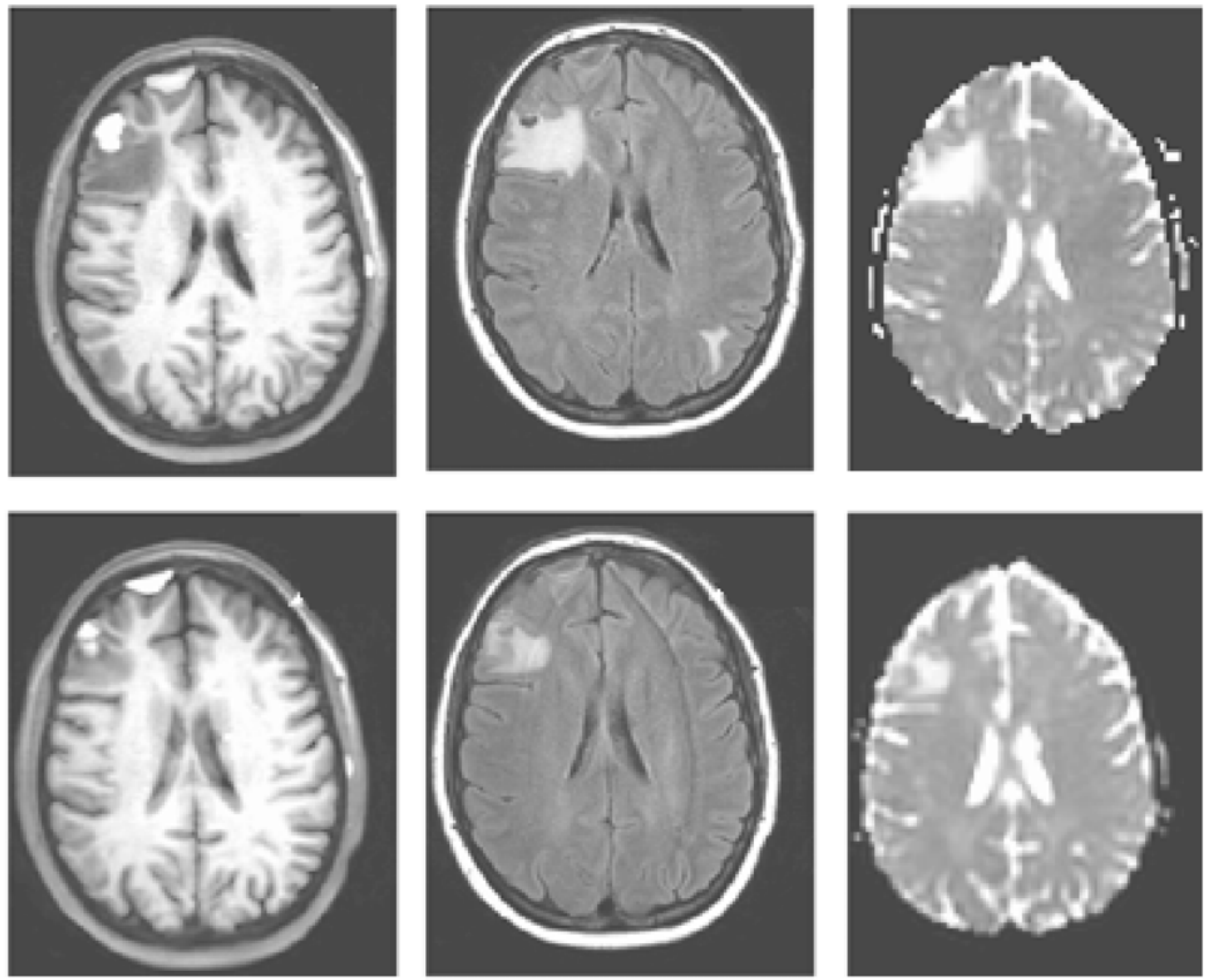
Response to Therapy

Patient 2

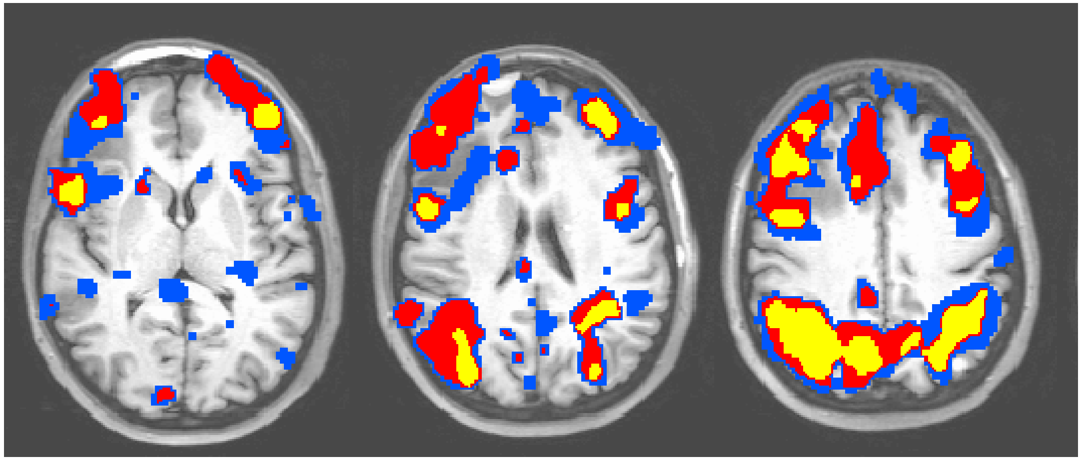
T1 | T2 FLAIR | ADC

Pre-Therapy

Post-Therapy

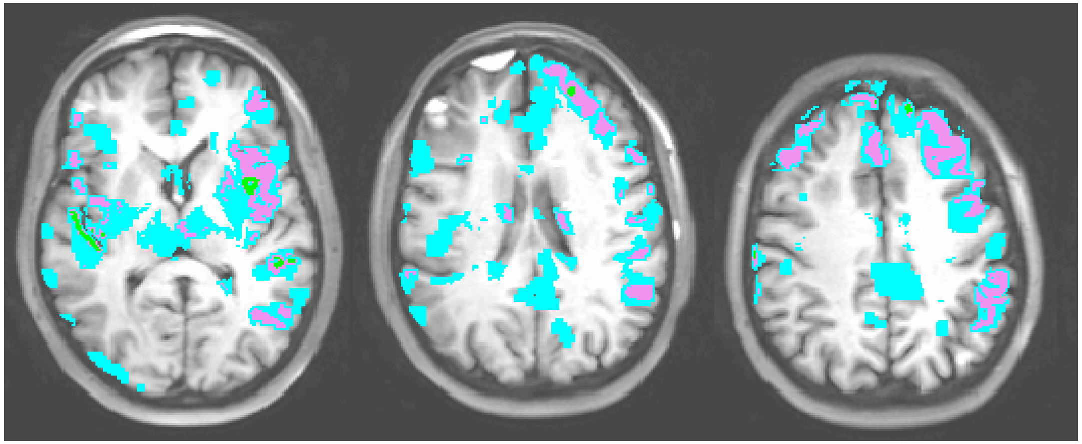


fMRI Results



N-Back: Working Memory

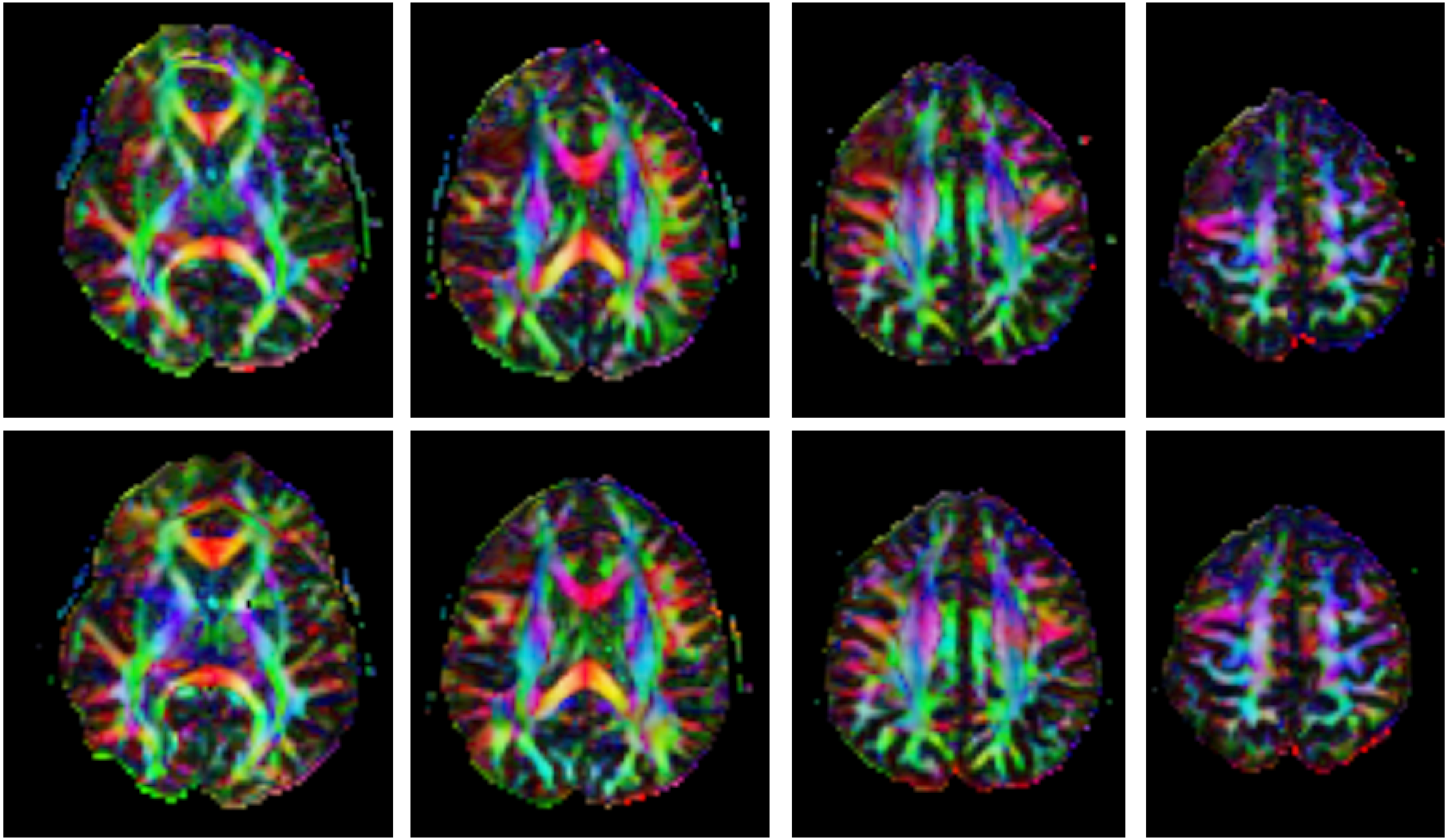
- Both Pre- and Post-Therapy
- Post-Therapy
- Pre-Therapy



Simon: Attention/Conflict

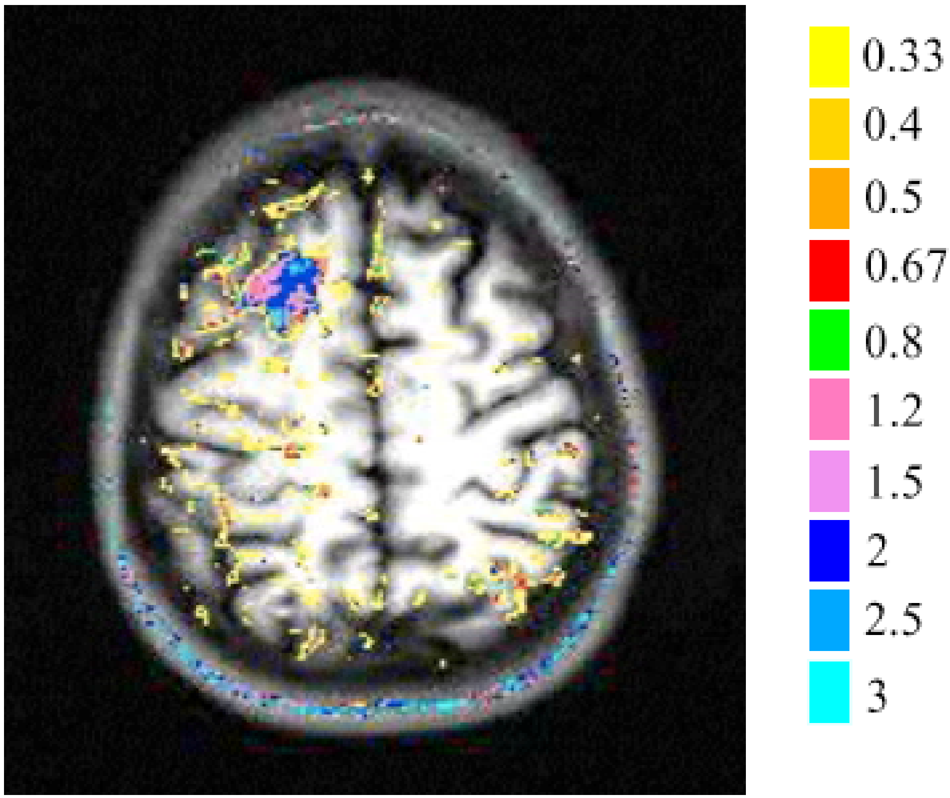
- Both Pre- and Post-Therapy
- Post-Therapy
- Pre-Therapy

Fractional Anisotropy



Brain Shift

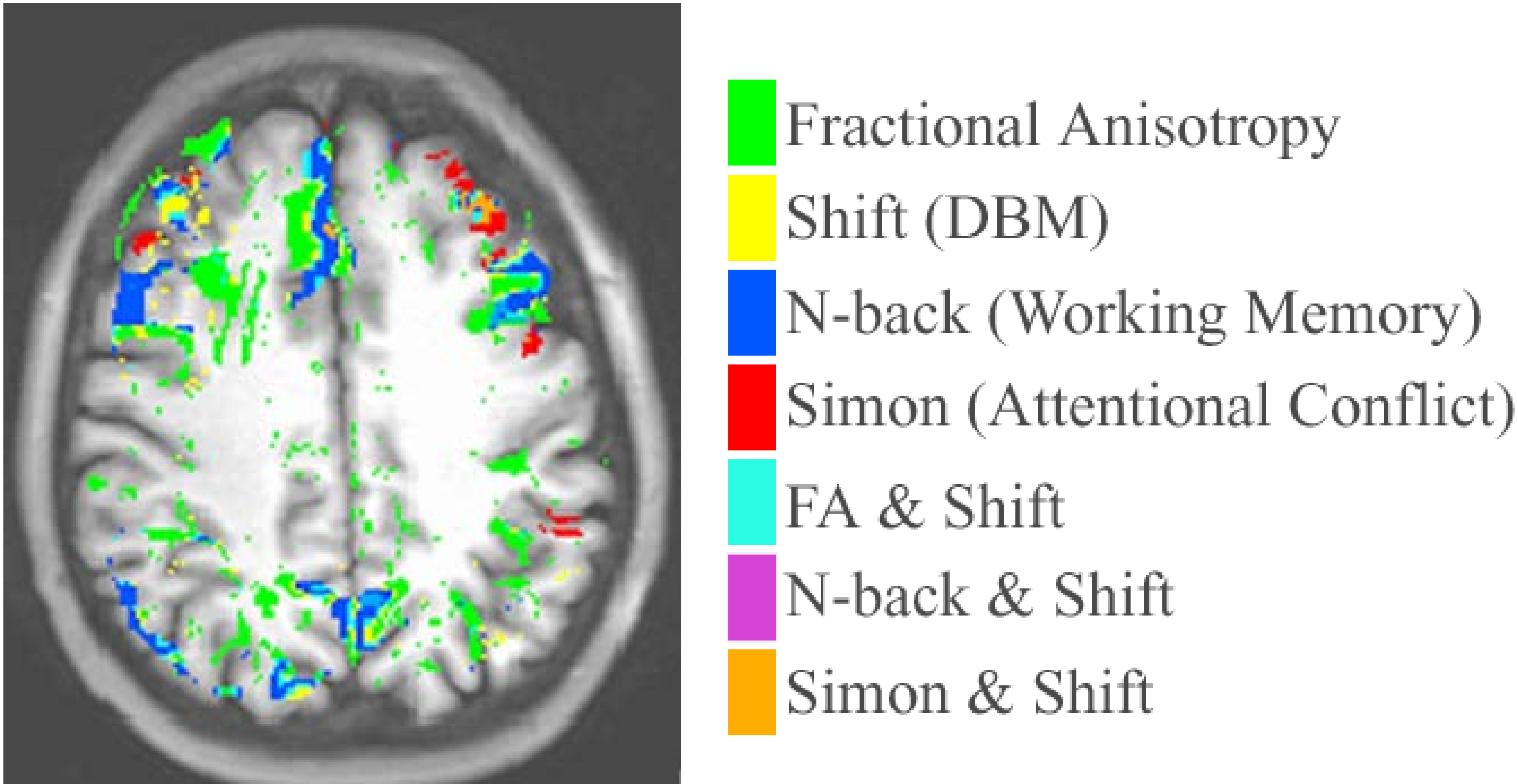
Deformation Based Morphometry



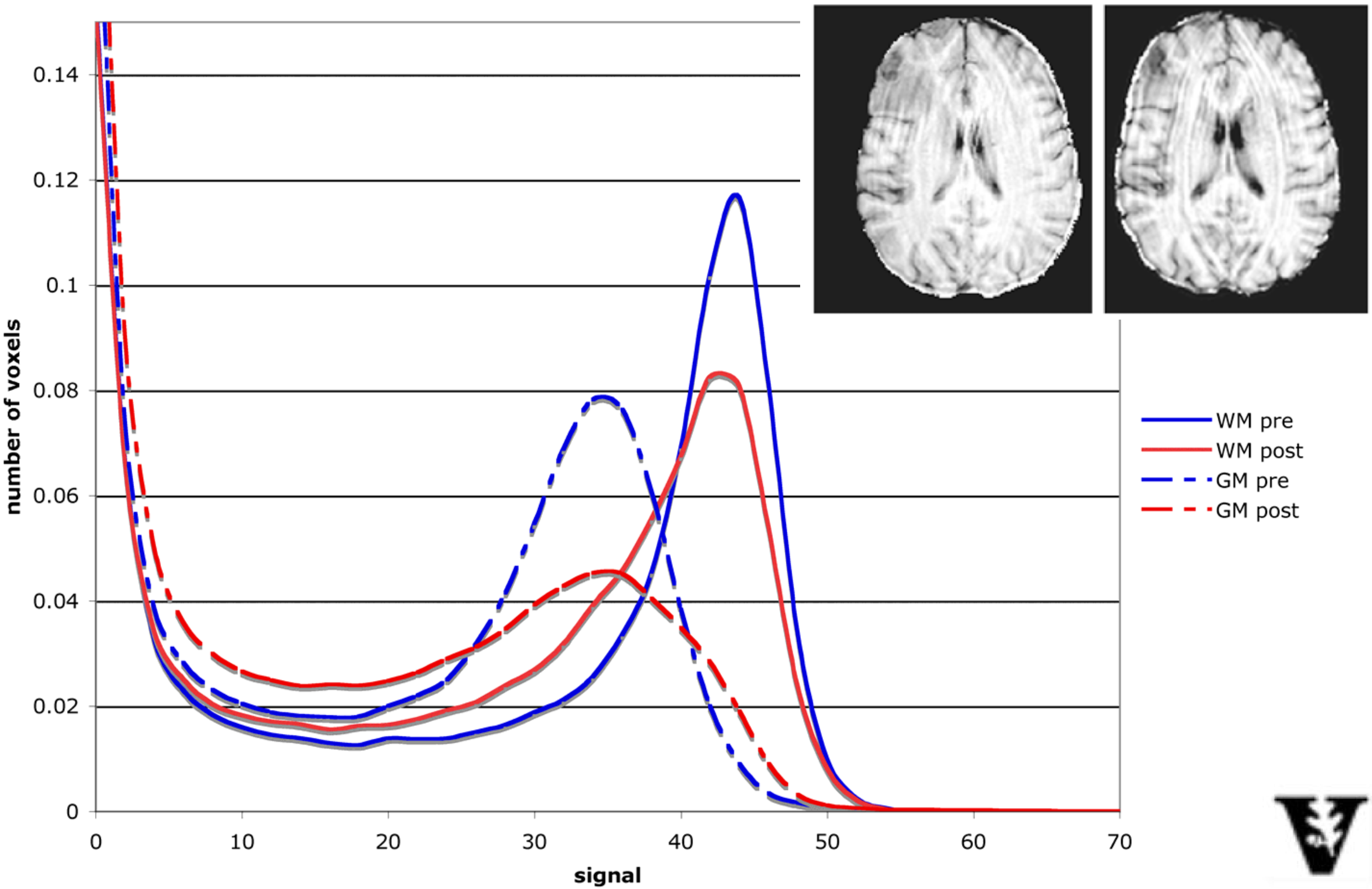
QuickTime™ and a
YUV420 codec decompressor
are needed to see this picture.

Riddle, et al. Ref..

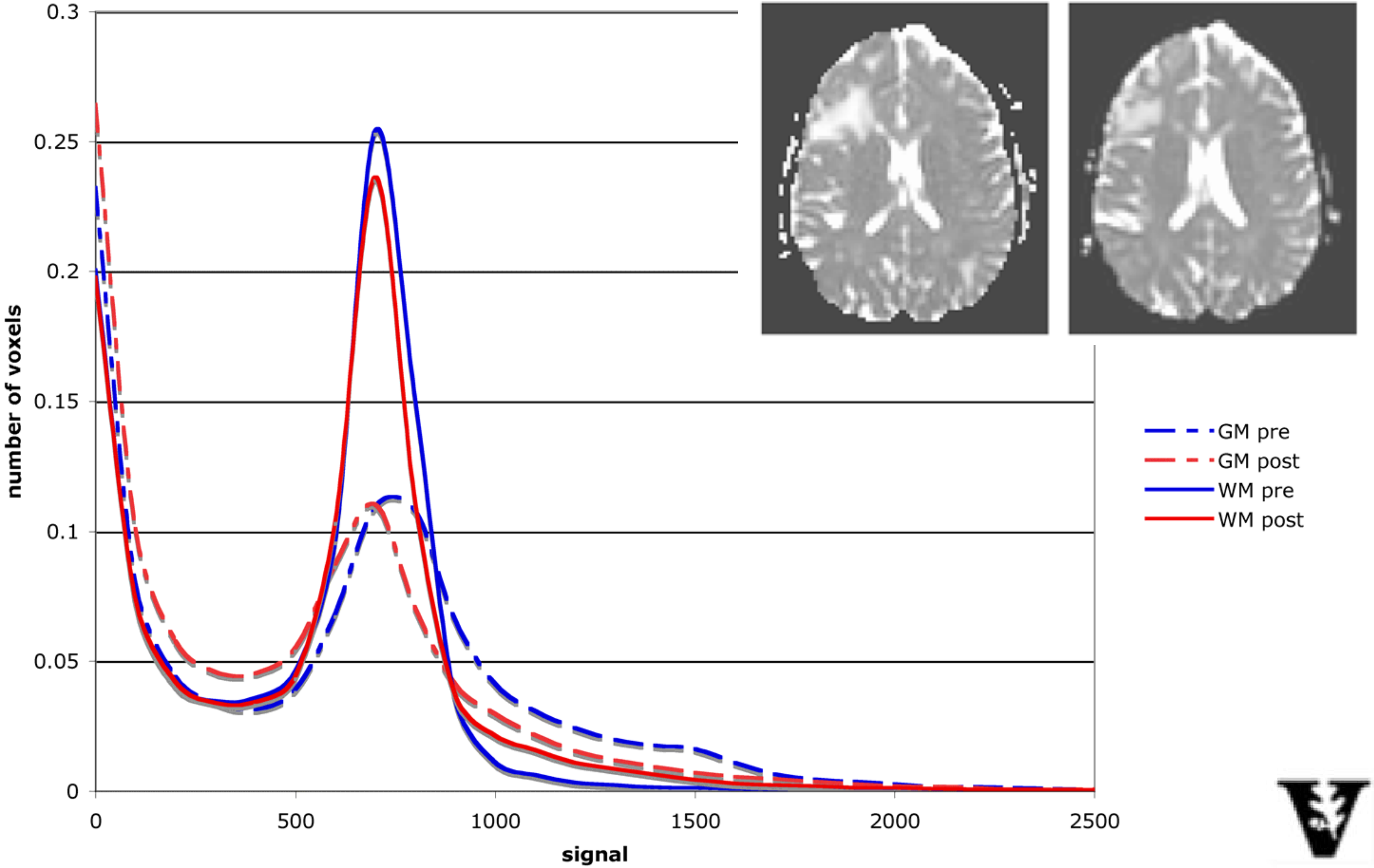
Composite Mapping



MTR Changes


0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
number of voxels
0
10
20
30
40
50
60
70
signal
WM pre
WM post
GM pre
GM post

ADC Changes

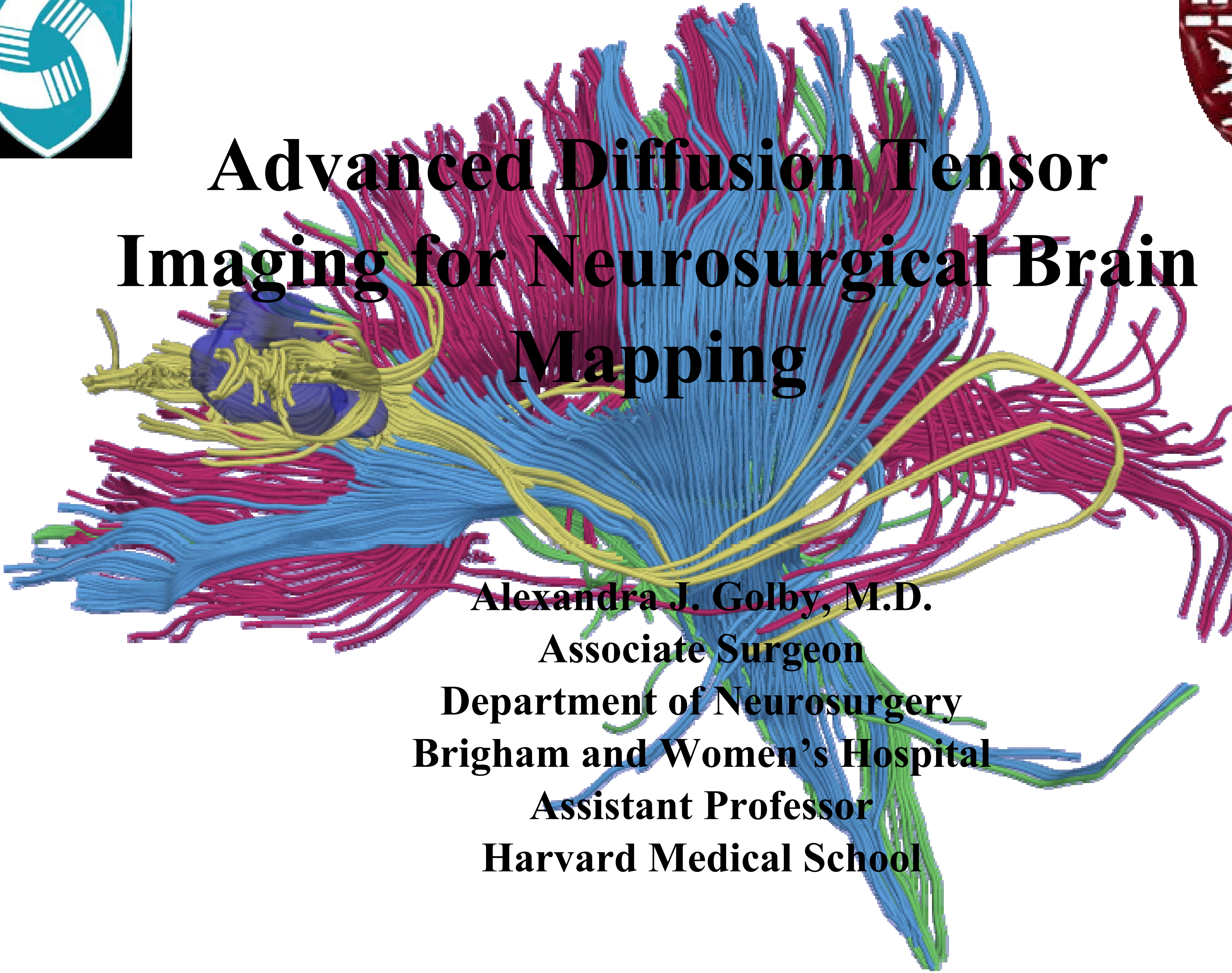


0.3
0.25
0.2
0.15
0.1
0.05
0
number of voxels
0
500
1000
1500
2000
2500
signal
GM pre
GM post
WM pre
WM post

Conclusions/Future Work

- Many more questions in a complicated disease state.
- Number of detailed case studies?
- Obvious goal - quality of life.
- Responses mixed - improvement of tumor burden, damage to cognitive ability.
- Tailor choice of paradigms to location of tumors.

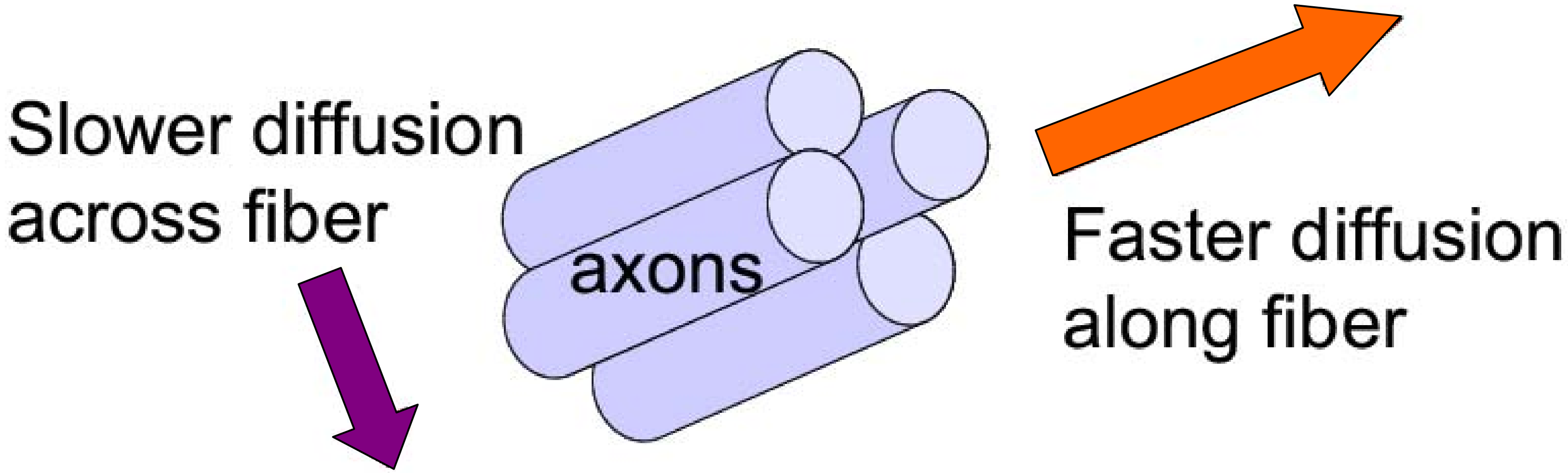
Advanced Diffusion Tensor Imaging for Neurosurgical Brain Mapping



Alexandra J. Golby, M.D.
Associate Surgeon
Department of Neurosurgery
Brigham and Women's Hospital
Assistant Professor
Harvard Medical School

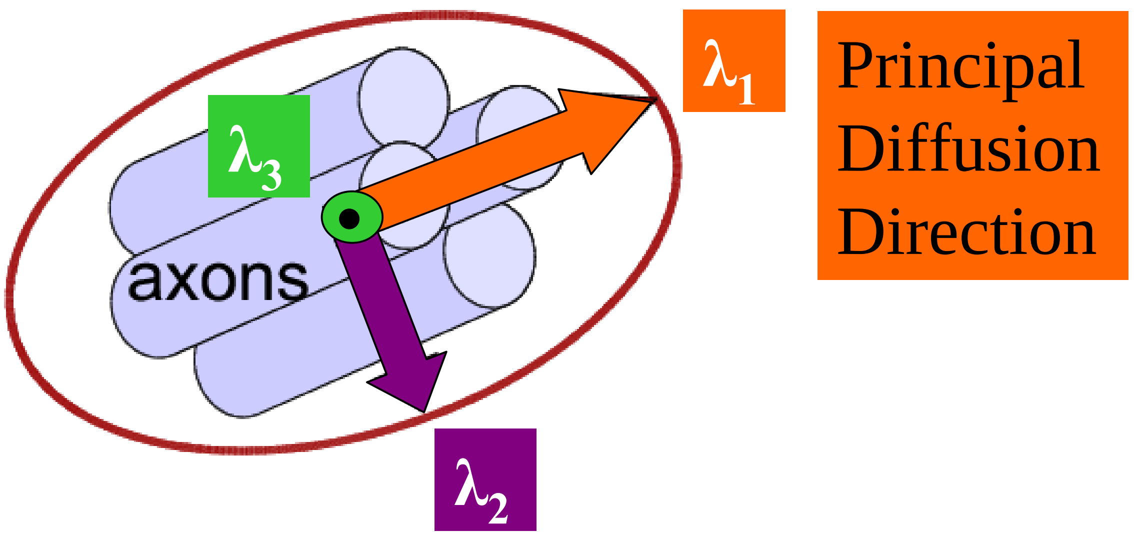
Diffusion MRI

- Only non-invasive measure of white matter tract structure



Diffusion Tensor MRI (DTI)

- Tensor model for diffusion
  - 3x3 symmetric, positive definite matrix
    - 3 eigenvalues and eigenvectors
  - Principal diffusion direction
    - assumed to align with tract

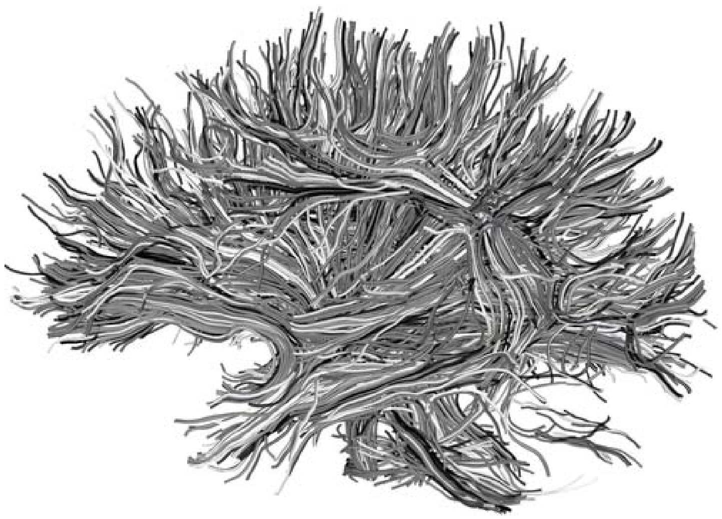


DTI Scientific Challenges for Neurosurgery

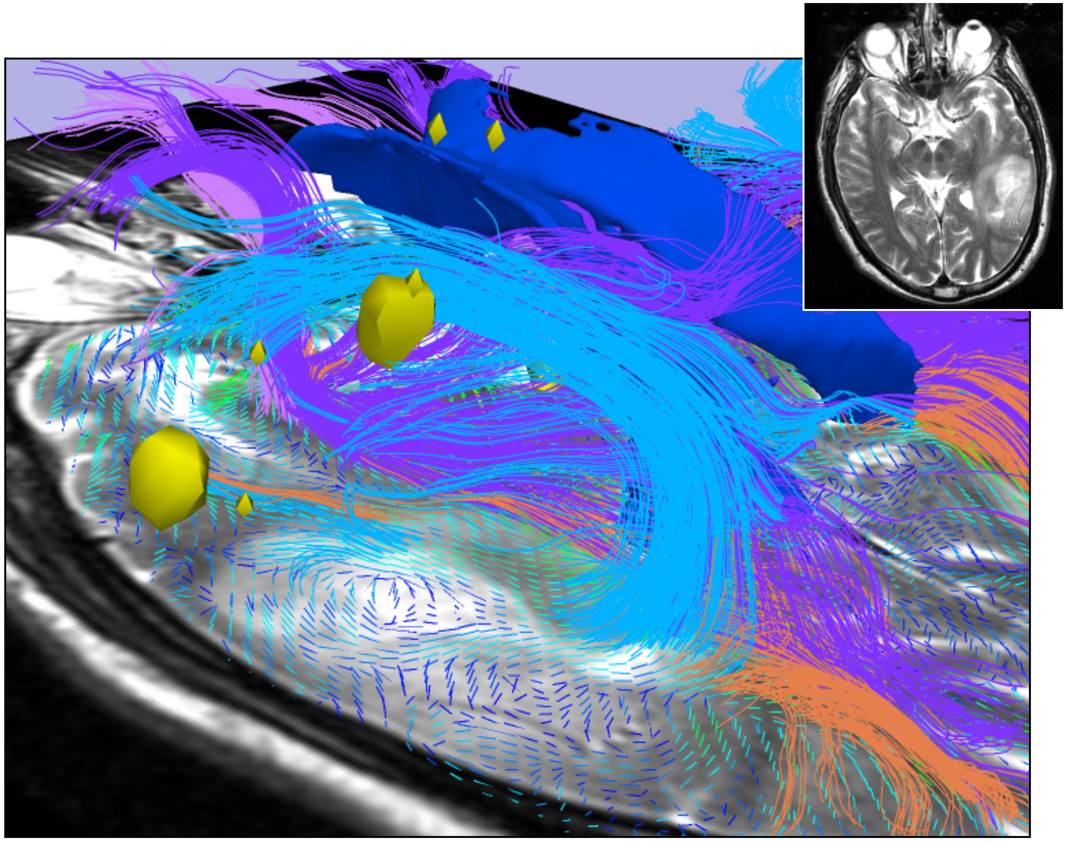
- Display of high-dimensional tensor data
  - Tractography clustering
- Non-informative in/near cortex
  - Tensor gradient approach to connecting fMRI/DTI
- Ambiguous in regions of fiber crossing
  - Two-tensor and stochastic tractography
- Correlation of DTI with pathology
  - Measure tumor effect along tracts
  - Develop high B-value scan

Displaying Tractography

- Fiber clustering



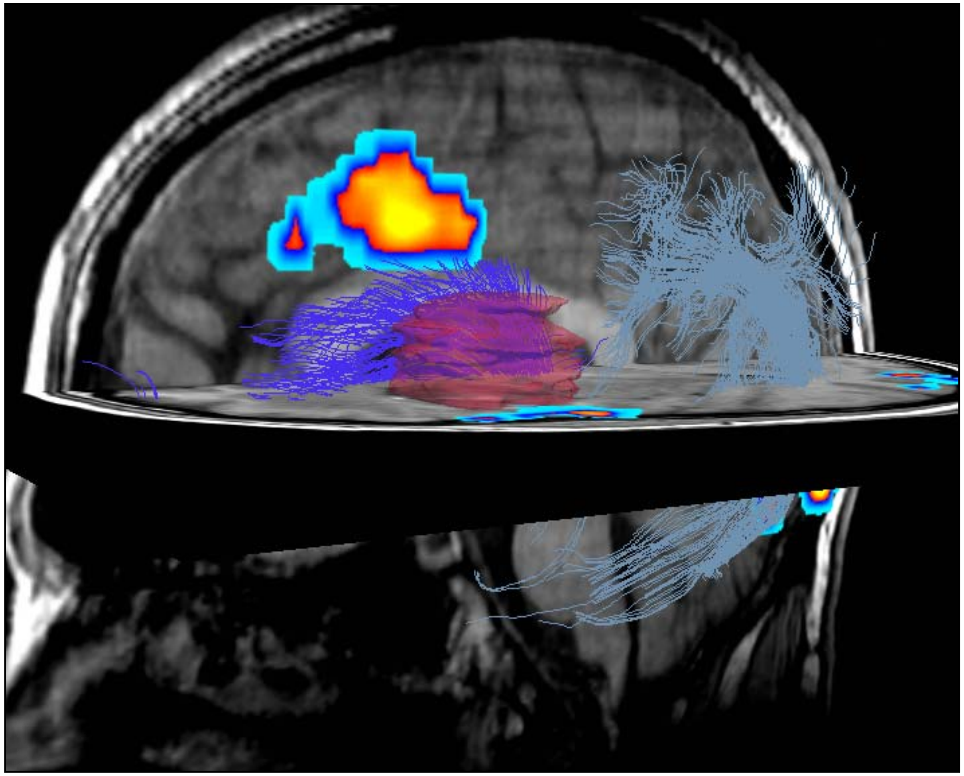
Whole brain tractography before clustering



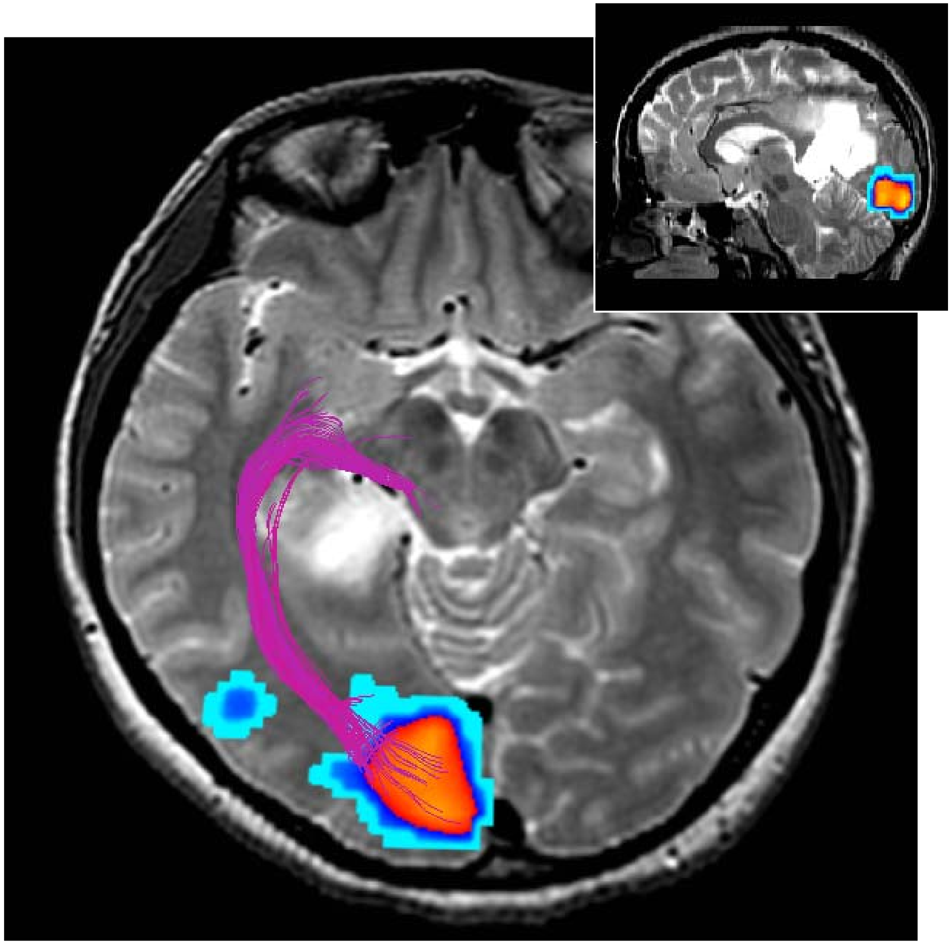
Clustering result in a surgical case: Arcuate fasciculus cluster near anaplastic astrocytoma

Lauren O'Donnell, Marek Kubicki, Martha E. Shenton, Mark E. Dreusicke, W. Eric L. Grimson, Carl-Fredrik Westin. *A Method for Clustering White Matter Fiber Tracts.* American Journal of Neuroradiology (AJNR) 27(5):1032-1036, 2006

Displaying Tractography



Glioblastoma

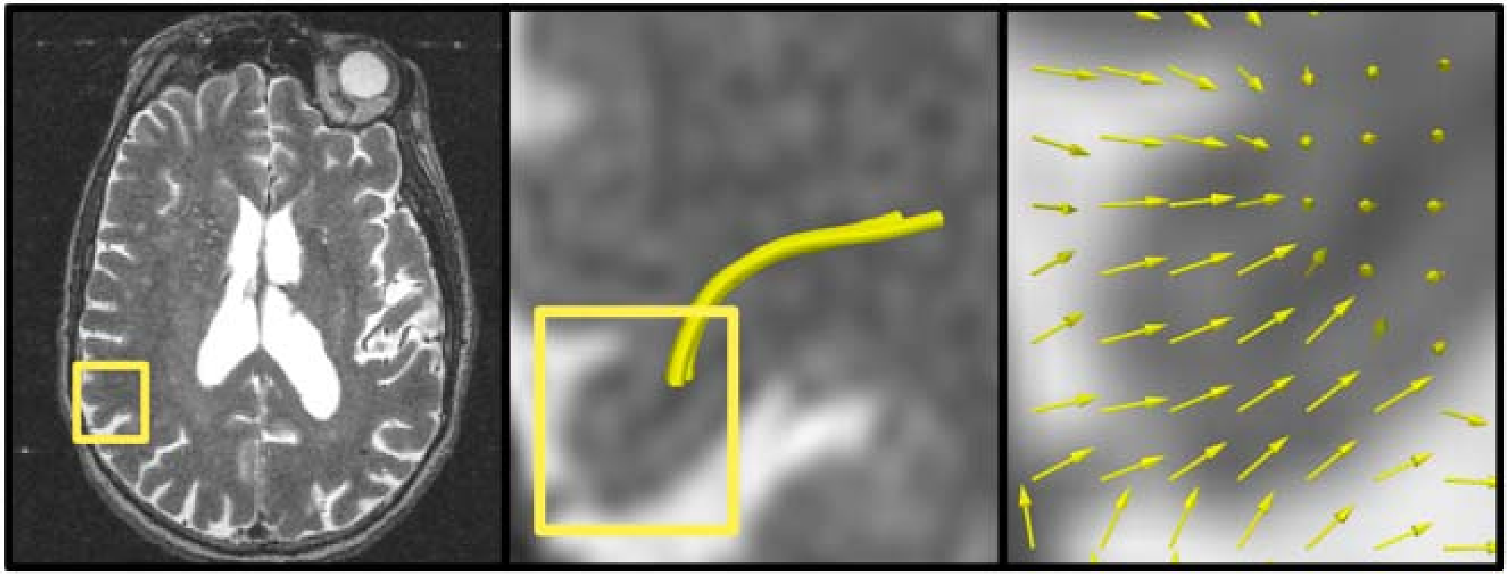


Low-grade Glioma

Lauren O'Donnell, Marek Kubicki, Martha E. Shenton, Mark E. Dreusicke, W. Eric L. Grimson, Carl-Fredrik Westin. *A Method for Clustering White Matter Fiber Tracts.* American Journal of Neuroradiology (AJNR) 27(5):1032-1036, 2006

fMRI and DTI: seeding from cortex

- Find white matter tract connecting to fMRI
  - Issue: cortical DTI is uninformative
- Follow tensor field gradients to reach tract

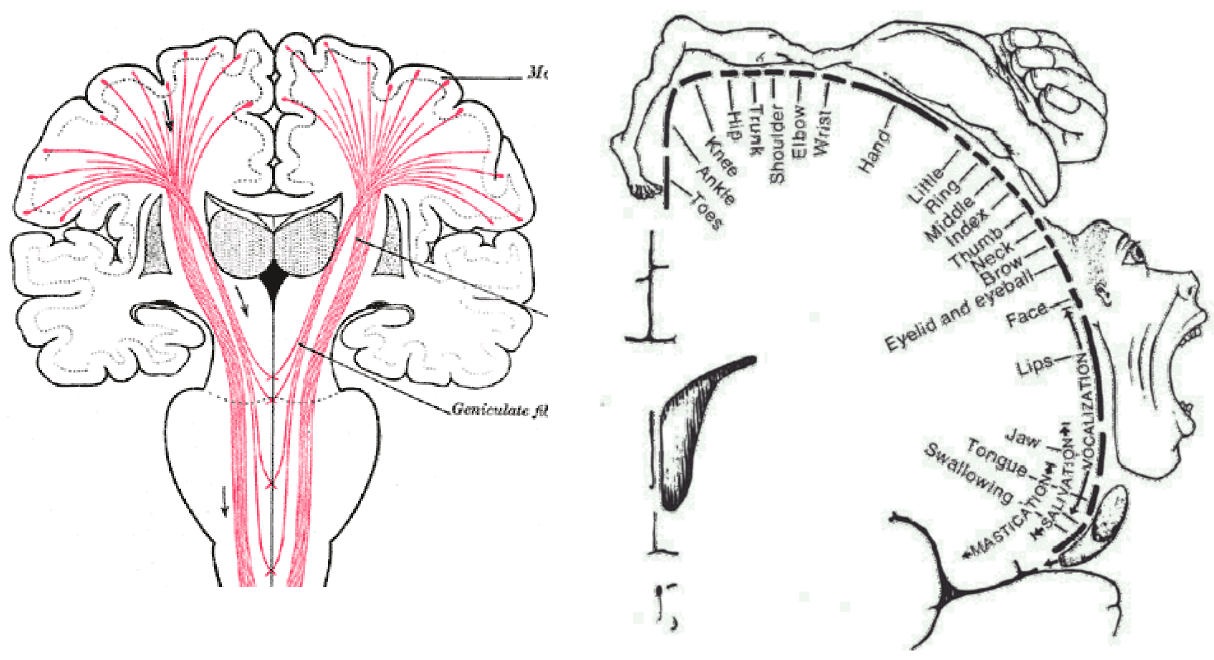


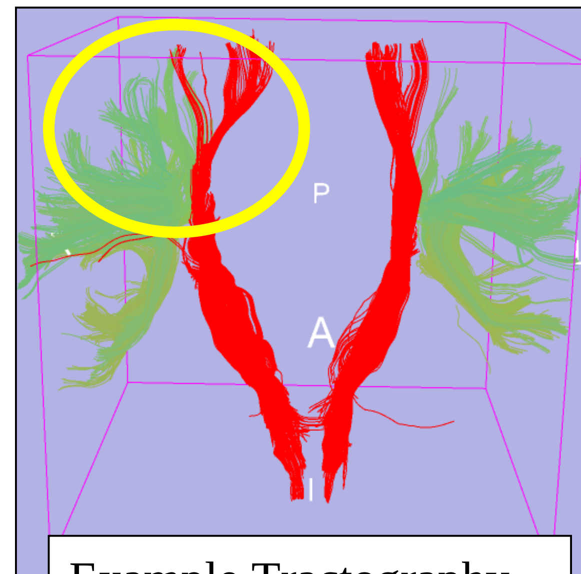
Anatomical Tractography Gradient of Tensor FA

DTI Tractography Challenge

- Fiber crossing can prevent tracking

Corticospinal Tract

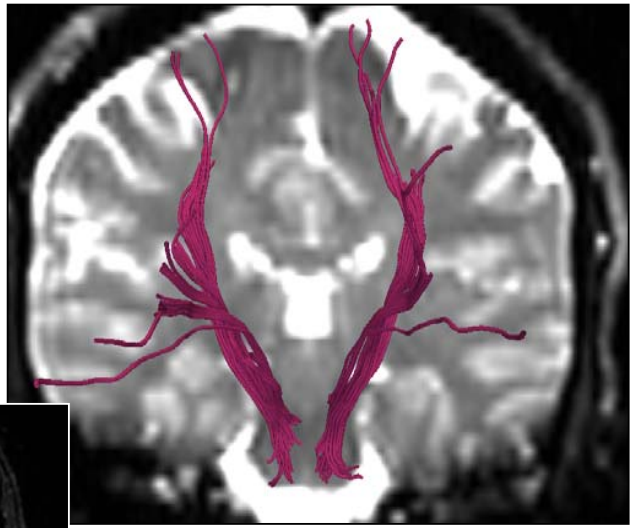


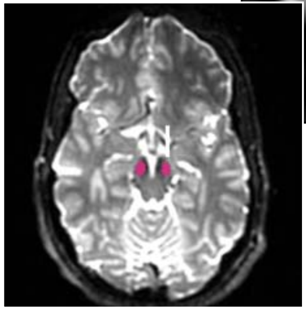


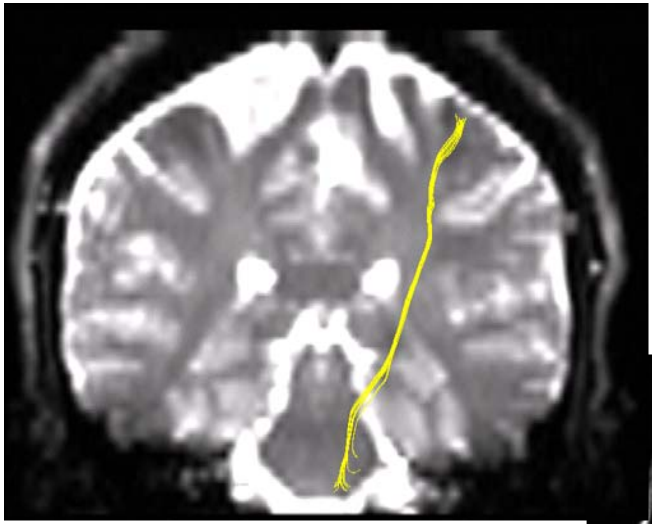
Example Tractography

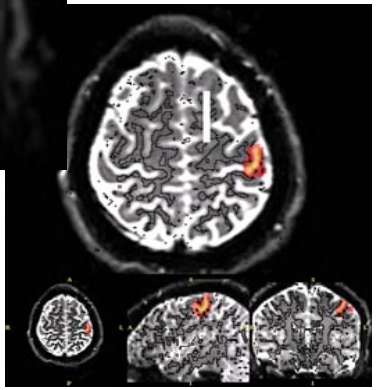
Single Tensor Tractography in CST

Brainstem ROI

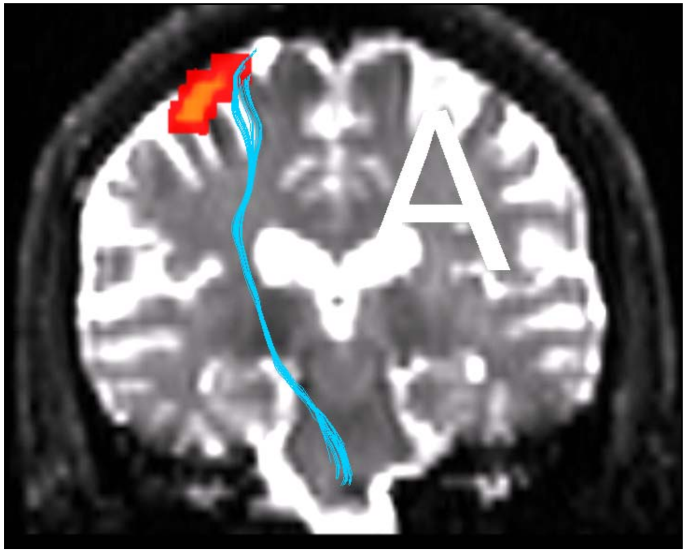








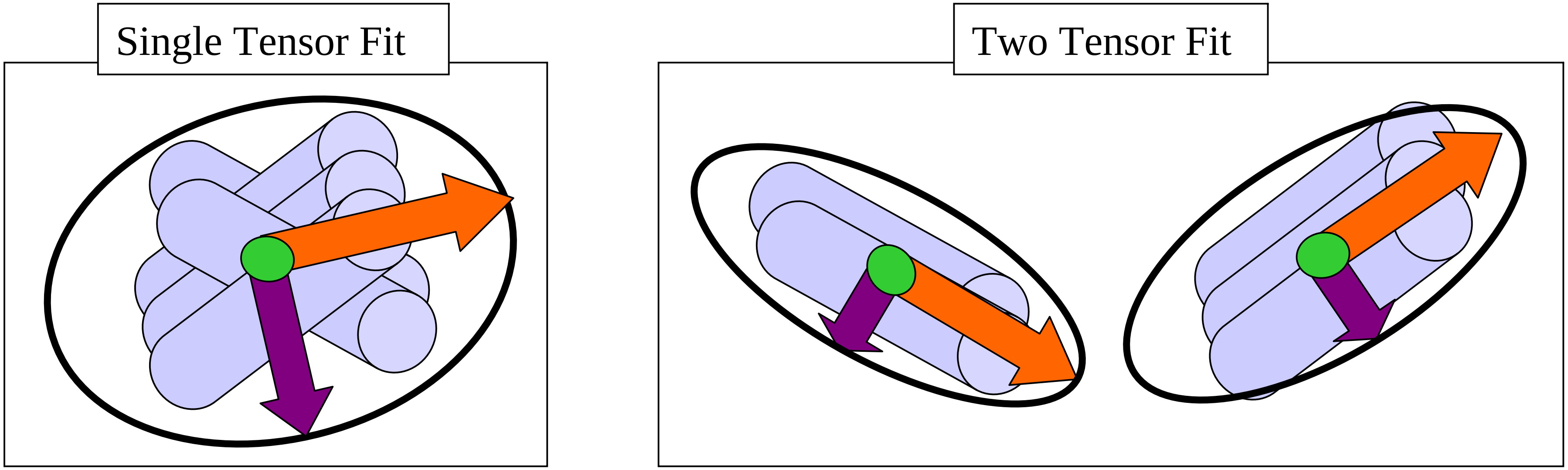
fMRI ROI



fMRI and Brainstem ROIs

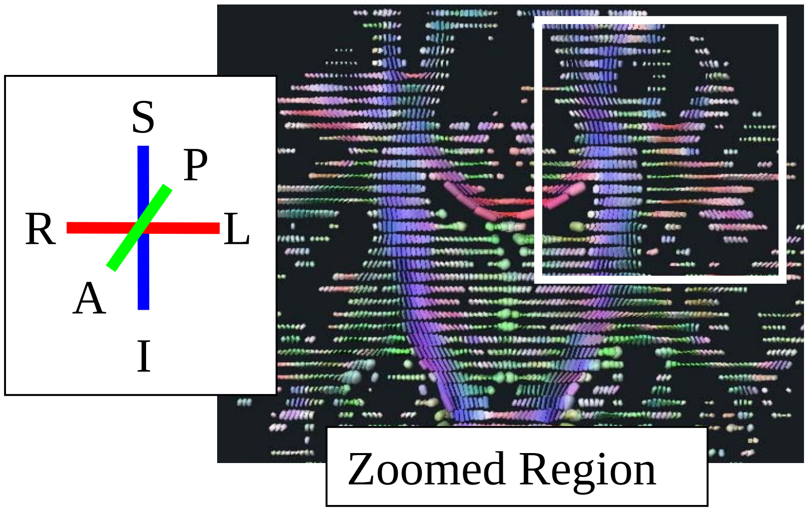
Two Tensor Model for Fiber Crossing

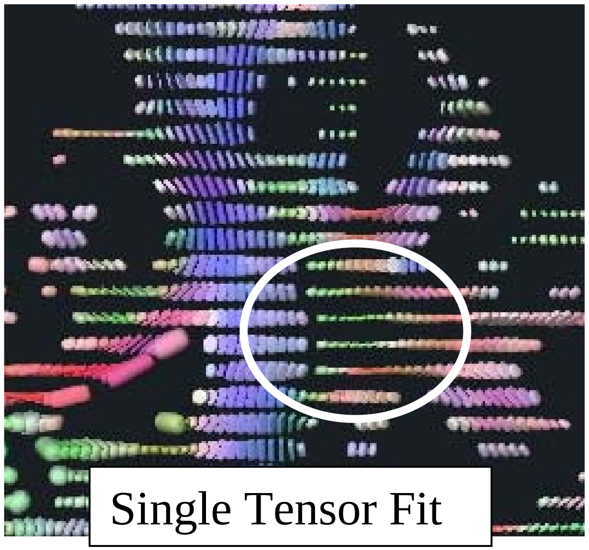
- Uses information from the single tensor fit
  - Decide where there should be two tensors
- Tractography is a challenge
  - Choose eigenvector similar to current direction

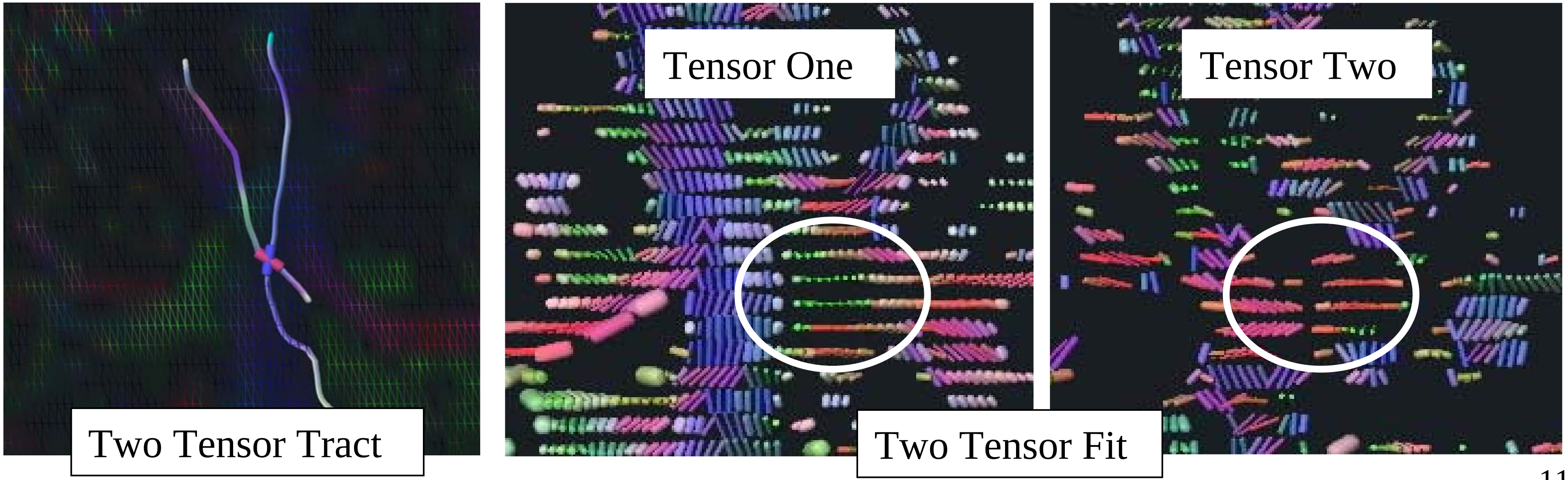


Sharon Peled, Ola Friman, Ferenc Jolesz, Carl-Fredrik Westin. **Geometrically constrained two-tensor model for crossing tracts in DWI**. Magnetic Resonance Imaging 2006;24:1263-1270.

Two Tensor CST Results

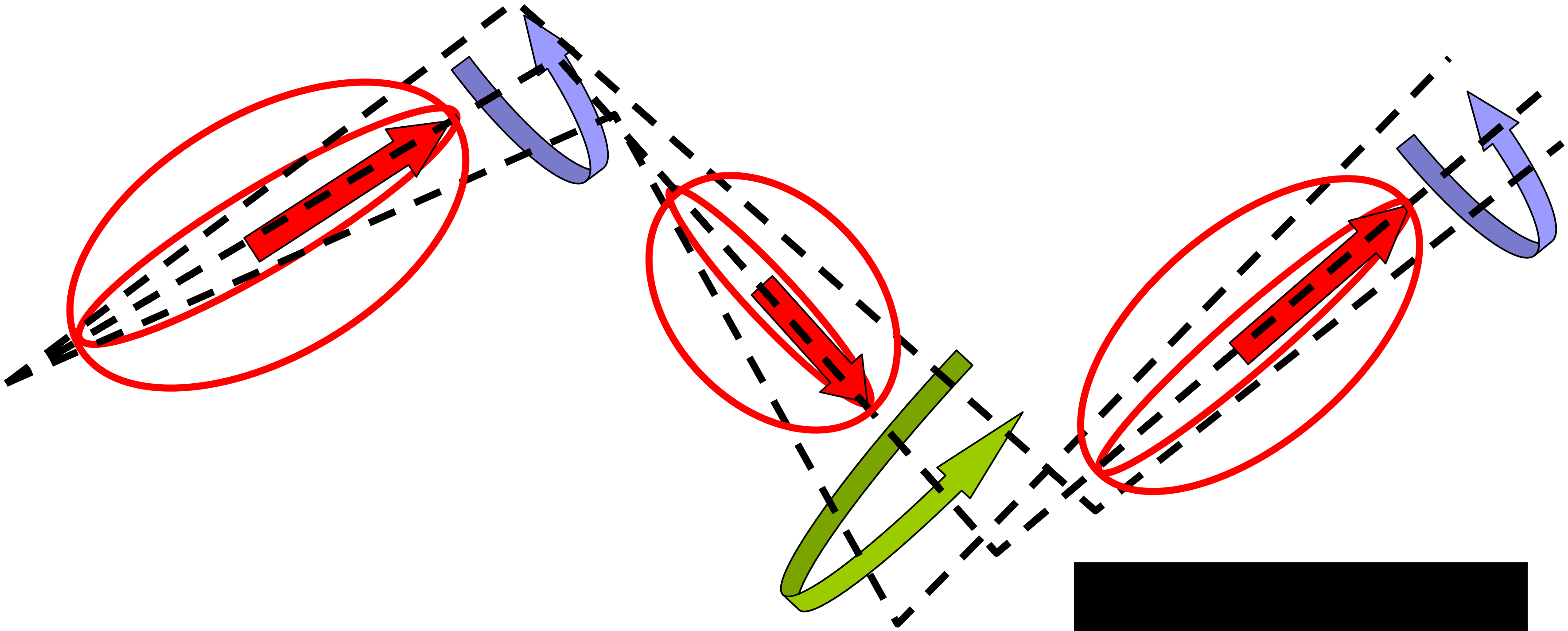




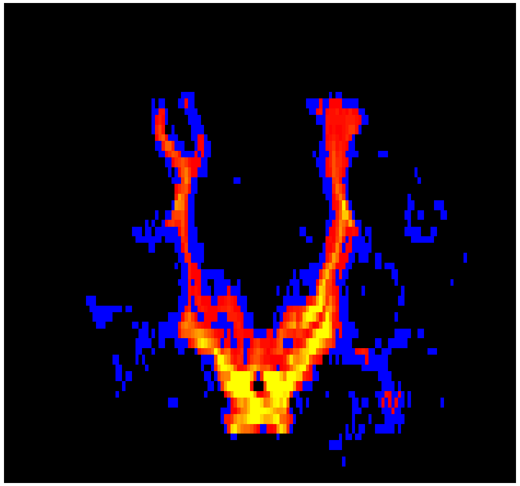


Images courtesy of Arish Asif Qazi and Gordon Kindlmann.

Stochastic Tractography



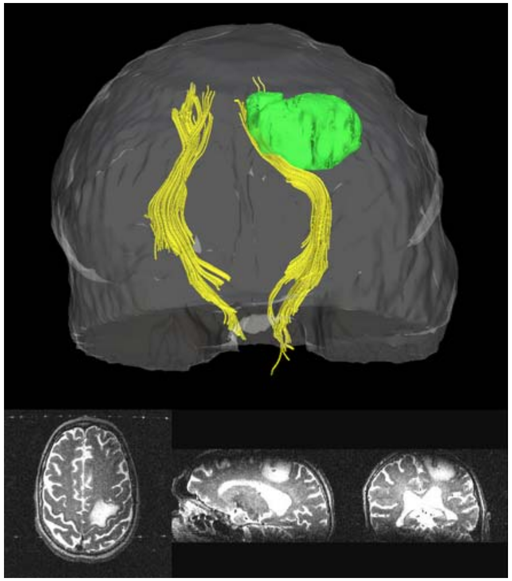
- Direction Uncertainty
  - DTI Noise
  - Crossing Fibers

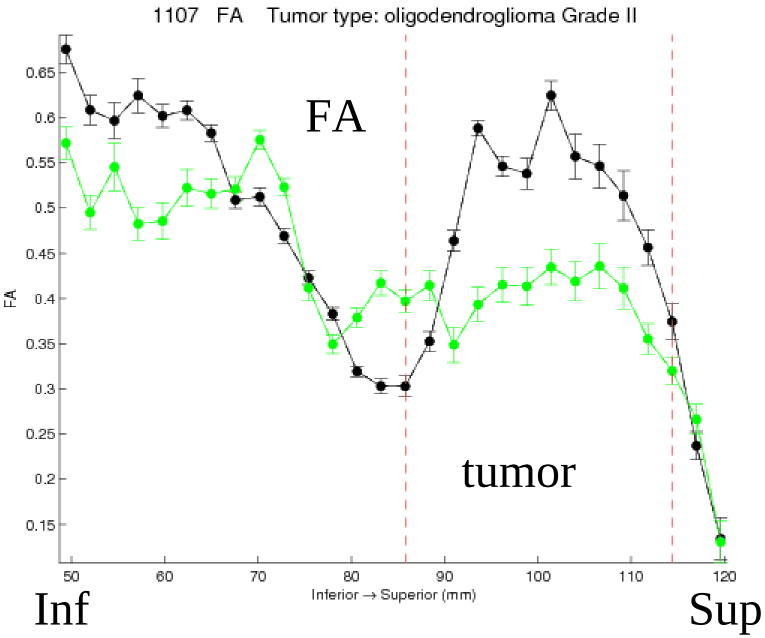


Images courtesy of Tri Ngo.

Pathophysiological Changes

- Quantify tumor effect along white matter tract
  - Infiltration/edema/displacement/compression



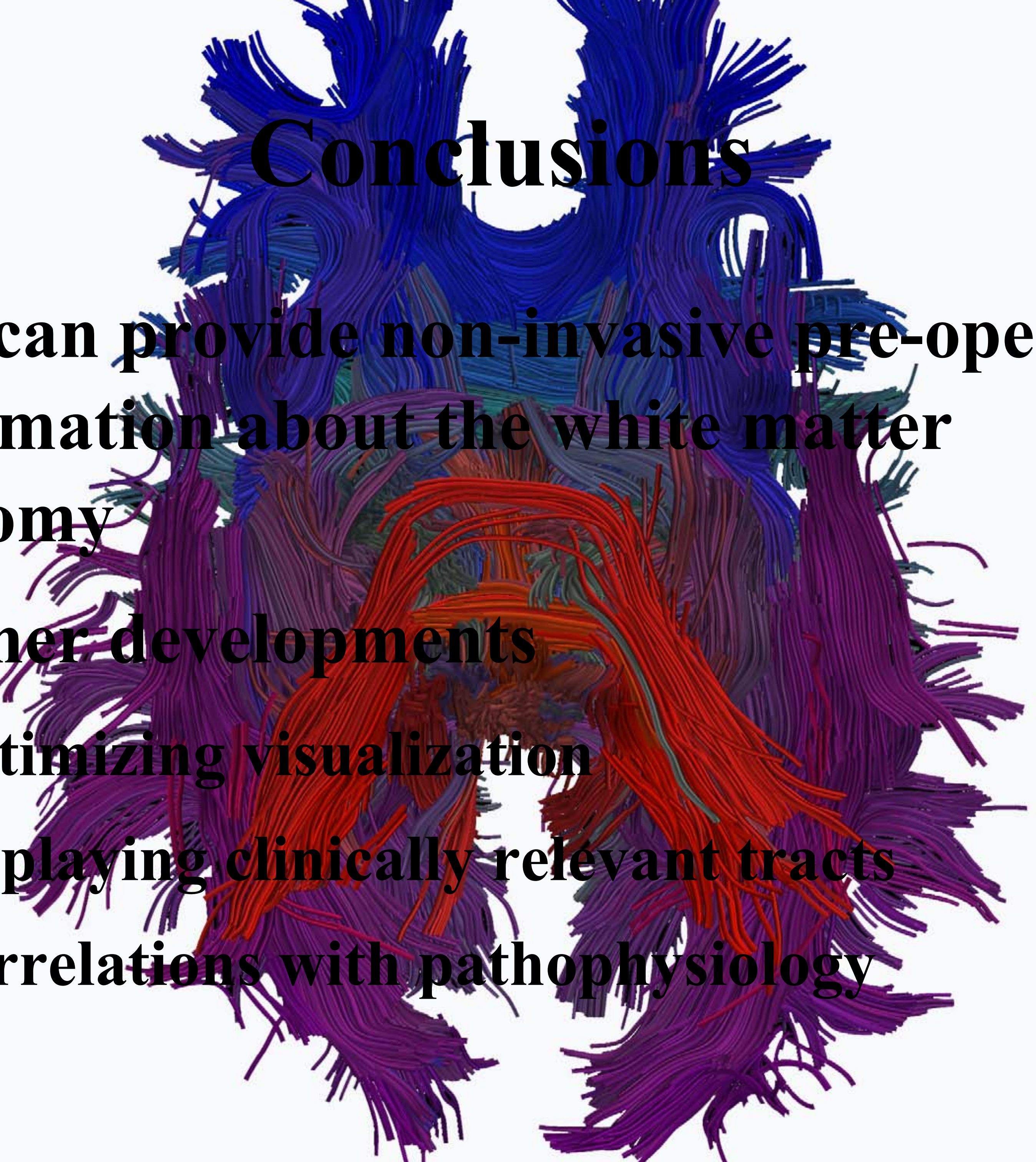


Monica E. Lemmond, Lauren J. O'Donnell, Stephen Whalen, Alexandra J. Golby. **Characterizing Diffusion Along White Matter Tracts Affected by Primary Brain Tumors**, HBM 2007
Lauren J. O'Donnell, Carl-Fredrik Westin, and Alexandra J. Golby. **Tract-Based Morphometry**, MICCAI 2007

Pathophysiological Changes

- Hypothesis: high b-value DTI can
  - differentiate edema and infiltrating tumor
  - enable tracking through edema
- Data acquisition: multiple diffusion directions and b-values
  - CURVE-ball (CUbe Rays to Vertices and Edges + isotropic spherical acquisition).
  - Novel and efficient clinically feasible method
- 12 patients scanned to date
- Investigating various analysis methods
  - to elicit tissue microstructural information
  - based on monte carlo simulations of diffusion

Sharon Peled. **New Perspectives on the Sources of White Matter DTI Signal**. In Press, IEEE Transactions on Medical Imaging



Conclusions

- DTI can provide non-invasive pre-operative information about the white matter anatomy
- Further developments
  - Optimizing visualization
  - Displaying clinically relevant tracts
  - Correlations with pathophysiology

Acknowledgments

- Neurosurgery
  - Peter Black, M.D., Ph.D.
  - Ian Johnson, M.D.
  - Dennis Oh, M.D.
- Radiology
  - Ferenc Jolesz, M.D.
  - Sharon Peled, Ph.D.
  - Carl Frederick Westin, Ph.D.
  - Lawrence Panych, Ph.D.
  - Sandy Wells, Ph.D.
  - Gordon Kindlemann, Ph.D.
  - Tri Ngo
- Neurology
  - Edward Bromifeld
  - Barbara Dworetzky
  - David McCarthy

Golby lab
  - Stephen Whalen, BS
  - Ralph Suarez, Ph.D.
  - Yan Mei Tie, Ph.D.
  - Lauren O'Donnell, Ph.D.
  - Isaiah Norton
  - James O'Shea, B.S.
  - Alireza Rezai, M.D.
  - Julie Levesque, B.A.

- U41RR019703 National Center for Image Guided Surgery
- NIH K08 NS048063
- Brain Science Foundation

Reconstruction of White Matter Tract Using Diffusion Tensor Imaging and its Application to Neurosurgery

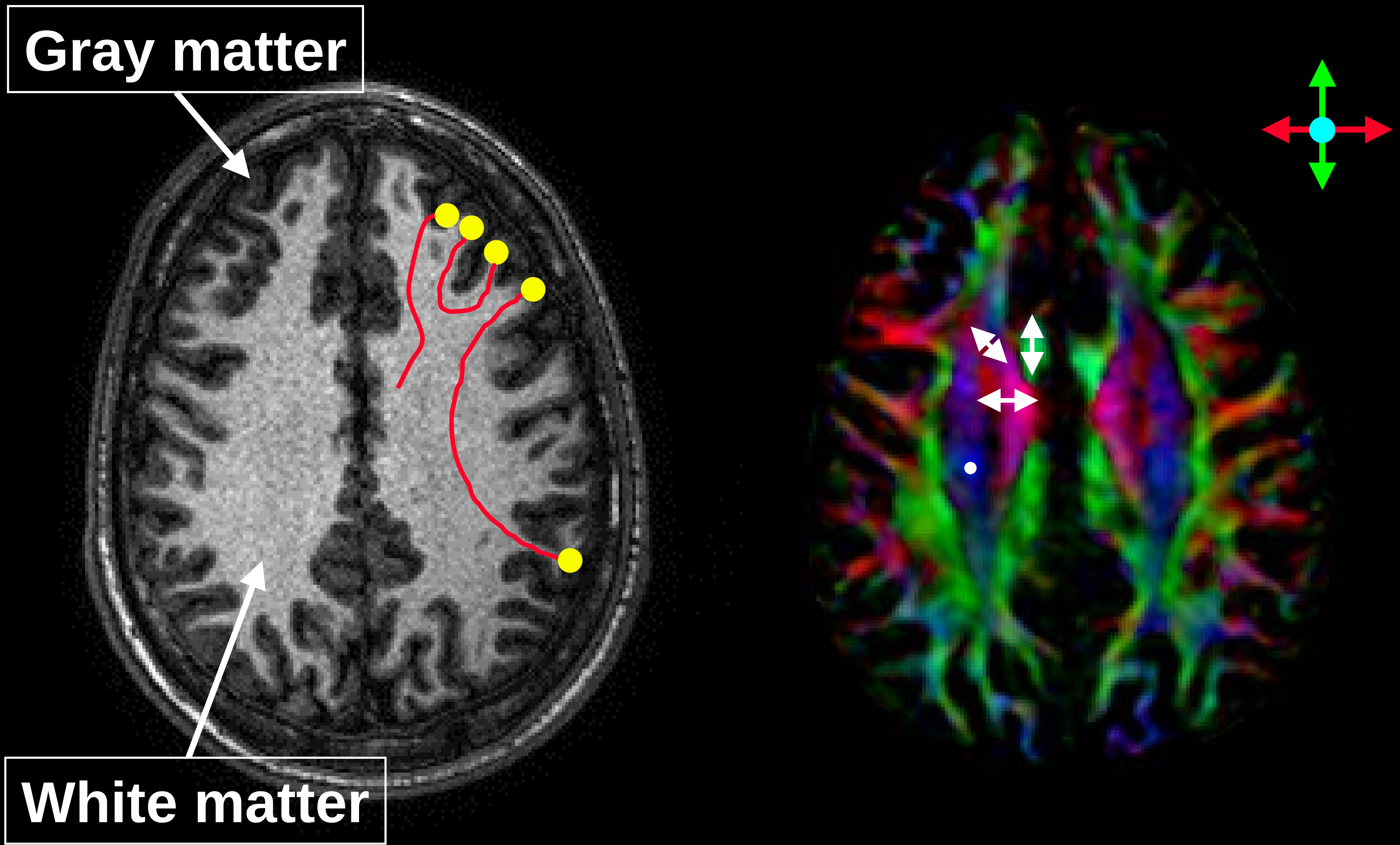
Susumu Mori

Johns Hopkins University Medical School

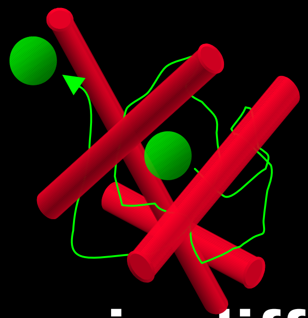
Content

- Principle of DTI
- Principle of tractography
- Application to brain tumor surgery

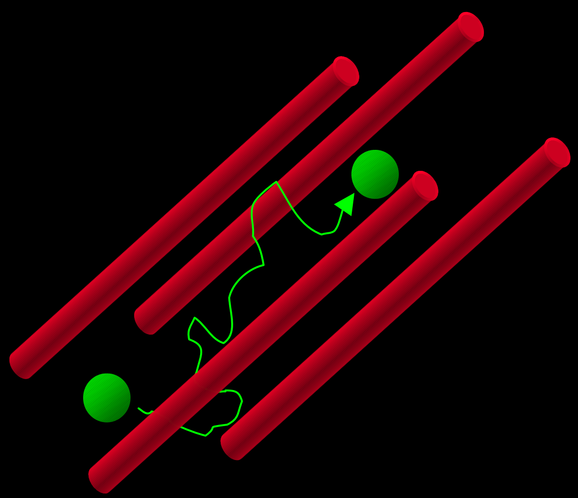
DTI reveals White matter anatomy



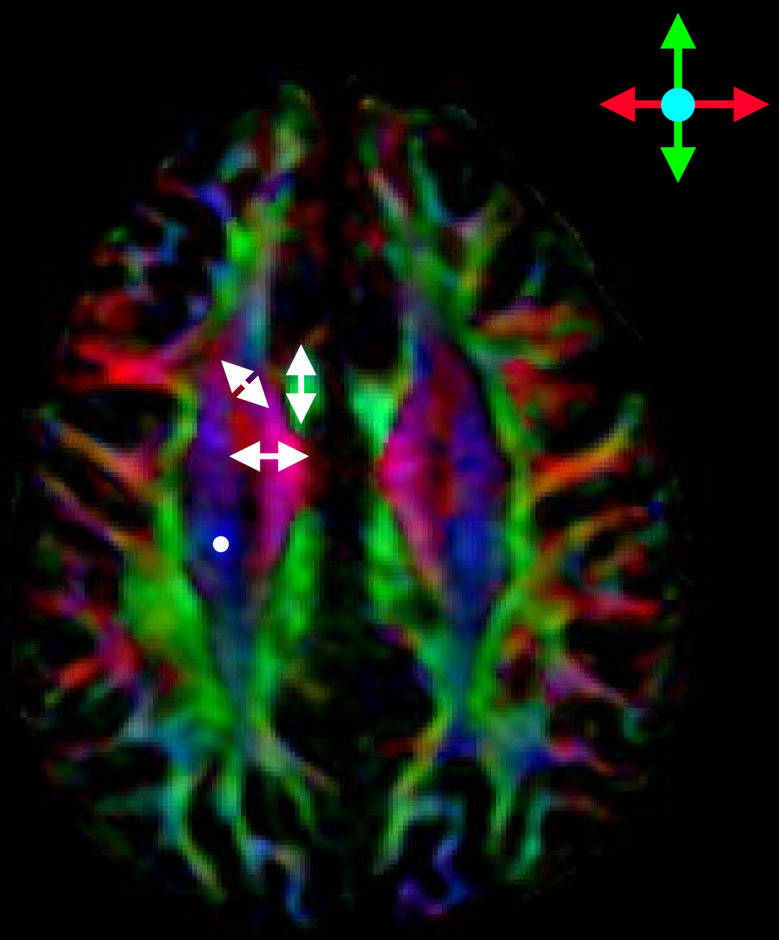
DTI uses water diffusion as a probe for white matter anatomy



Isotropic diffusion



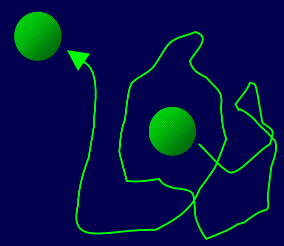
Anisotropic diffusion

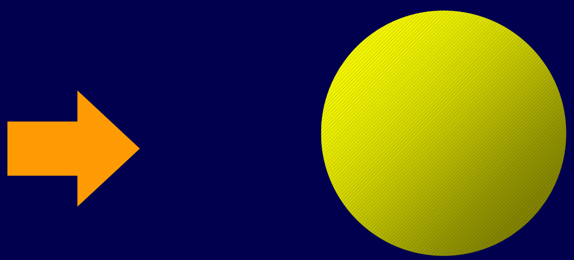


Anisotropic diffusion

Free diffusion

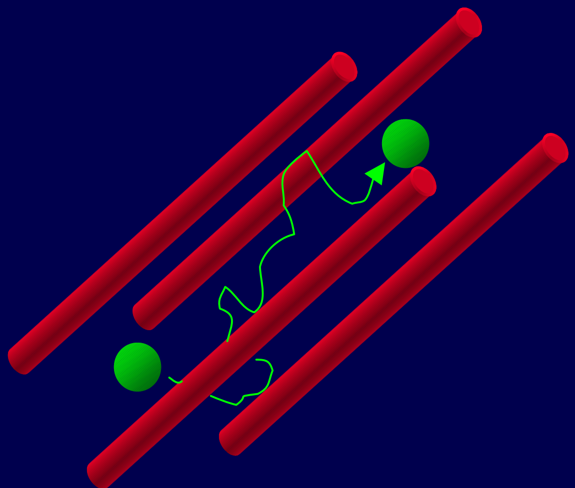
Isotropic diffusion

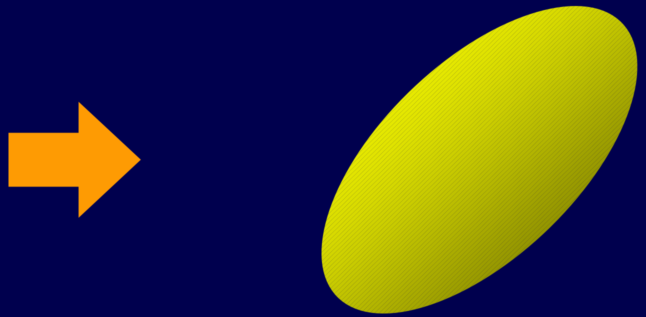




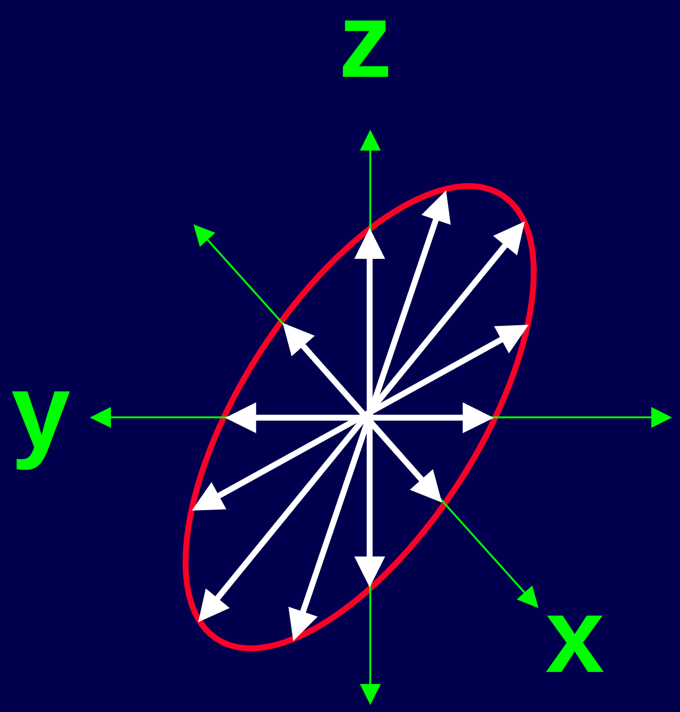
Restricted diffusion

Anisotropic diffusion

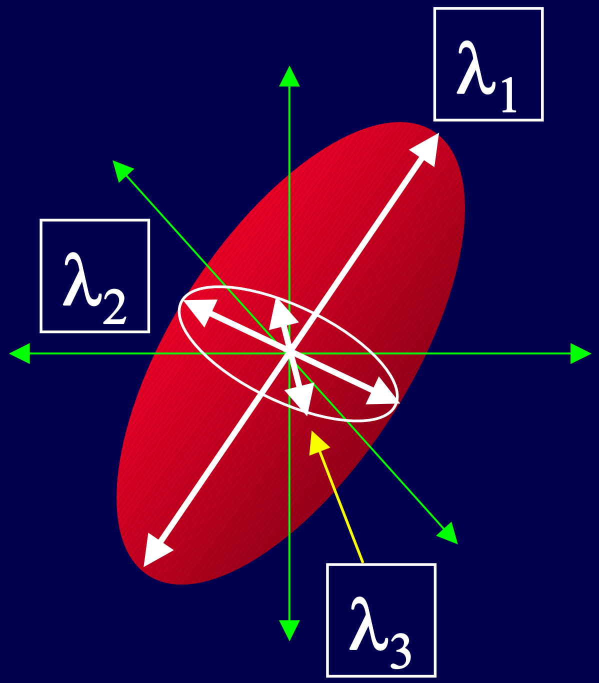




Characterization of diffusion

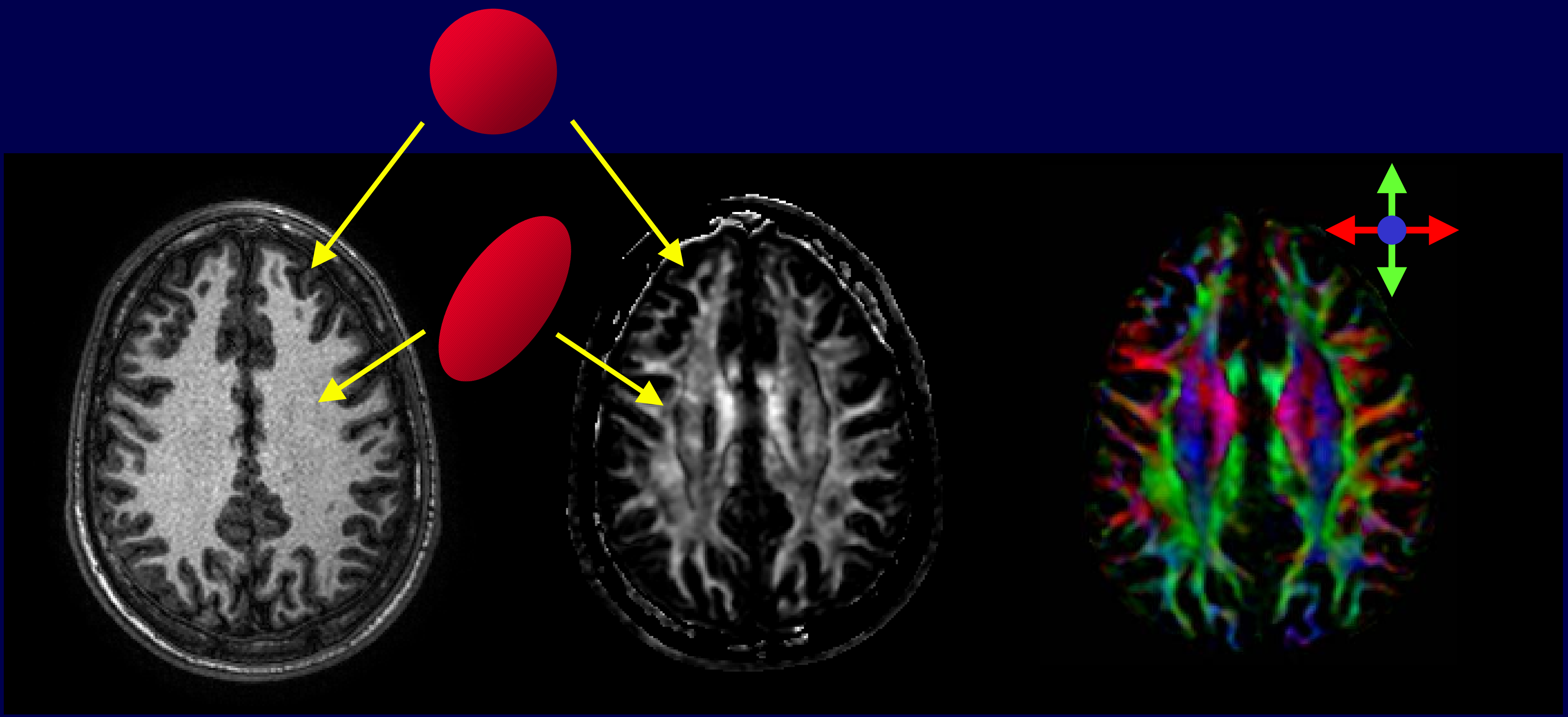


Measure diffusion along various directions (> 6)

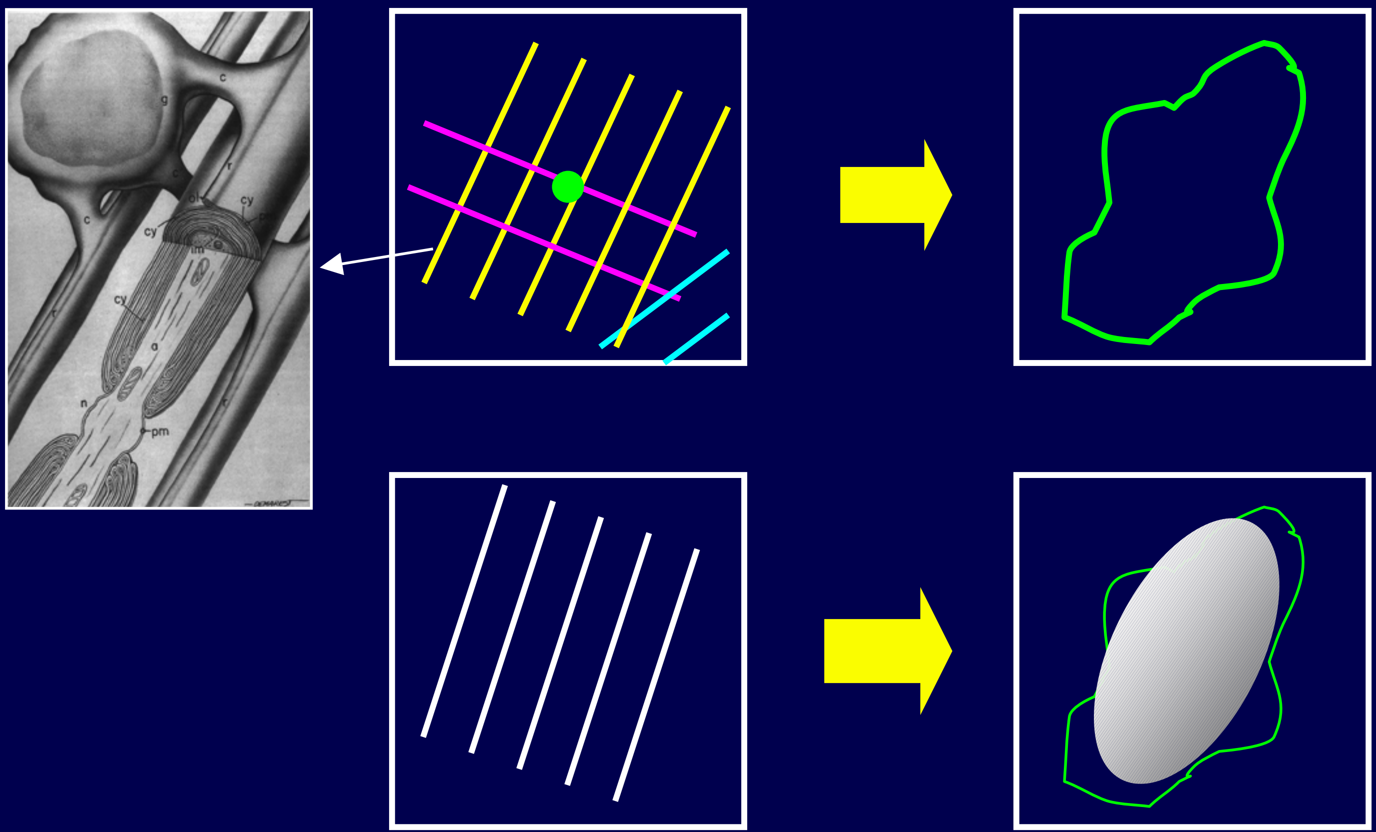


Calculate shape of the ellipsoid

Tensor map, anisotropy map, and color-coded orientation map

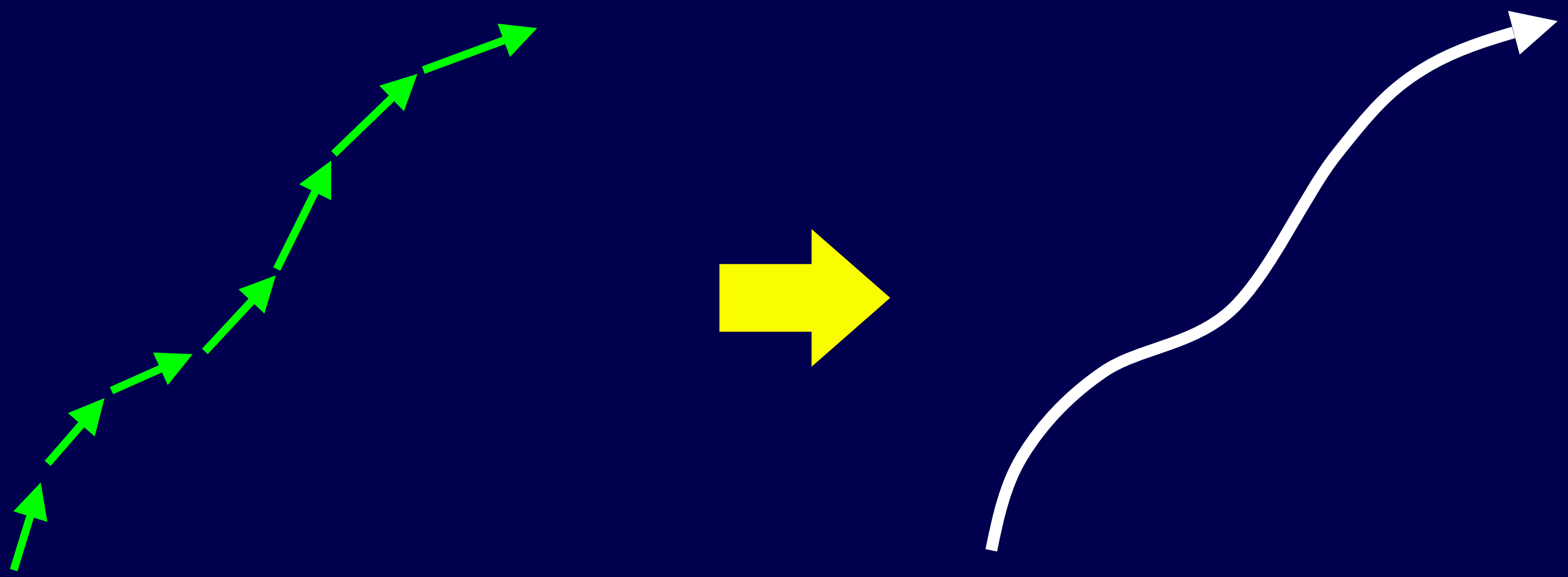


Simplifications and assumptions in DTI



Diffusion ellipsoid

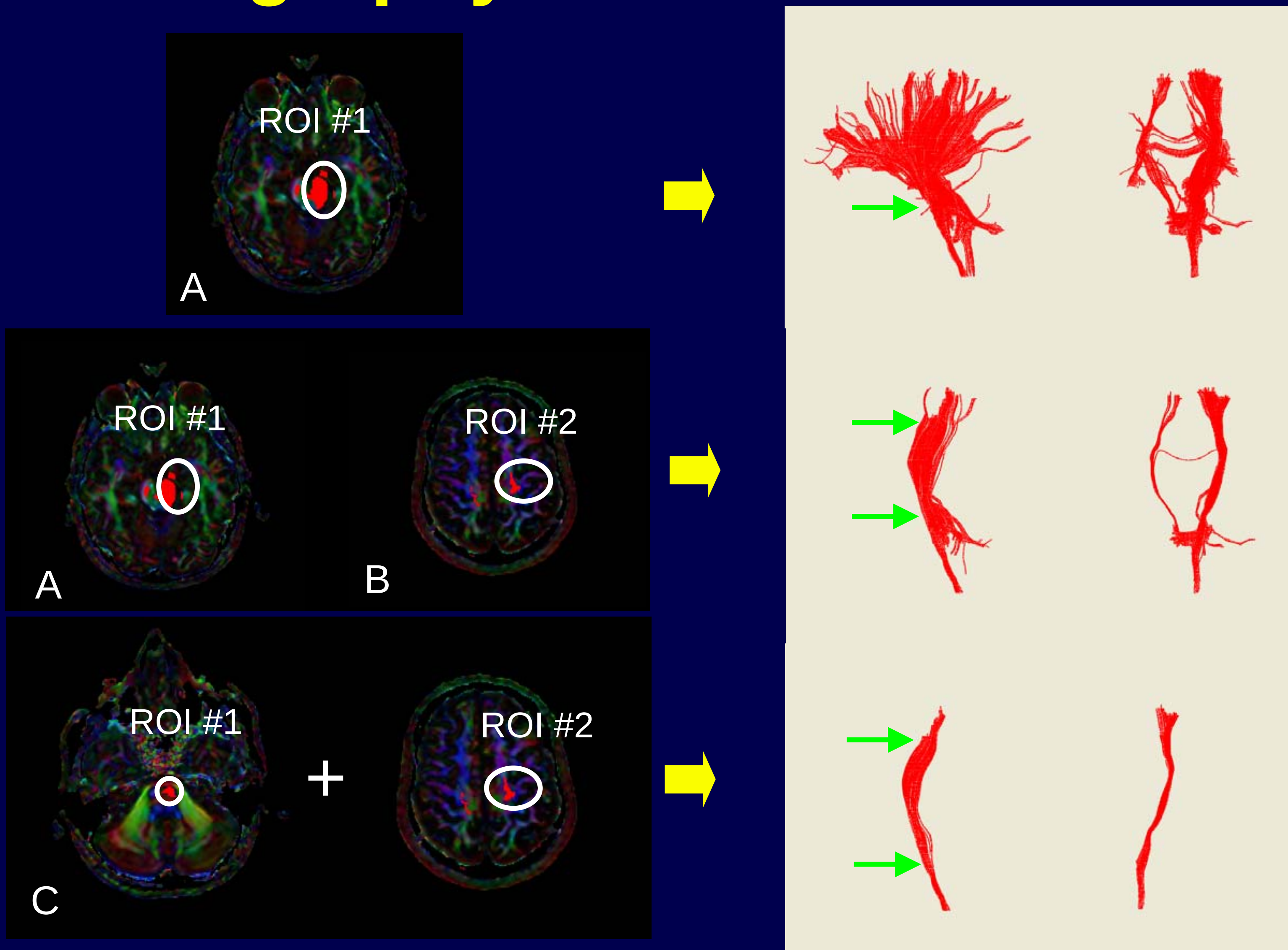
Can axonal projections be reconstructed?



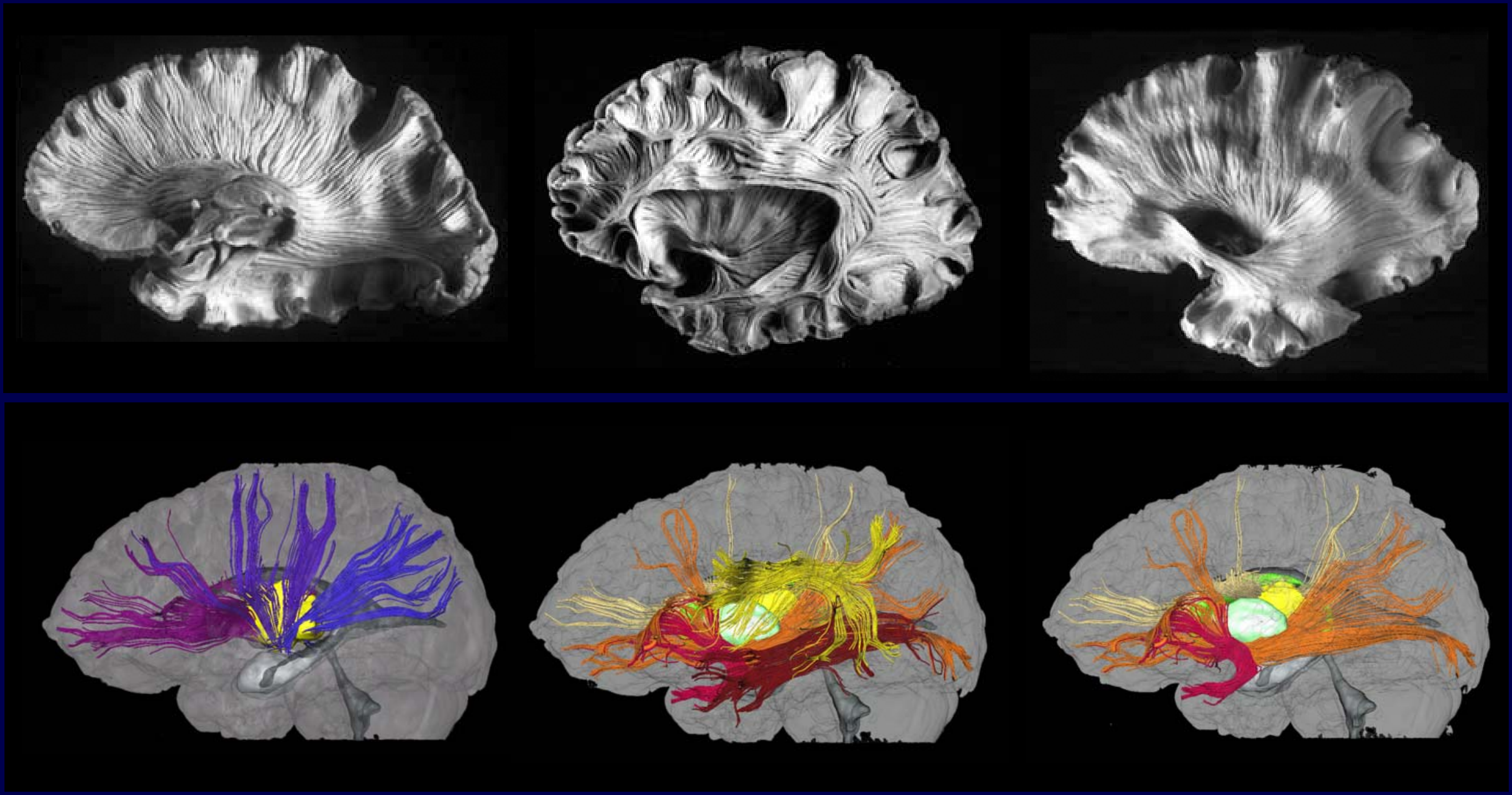
At each voxel, average fiber orientation can be estimated

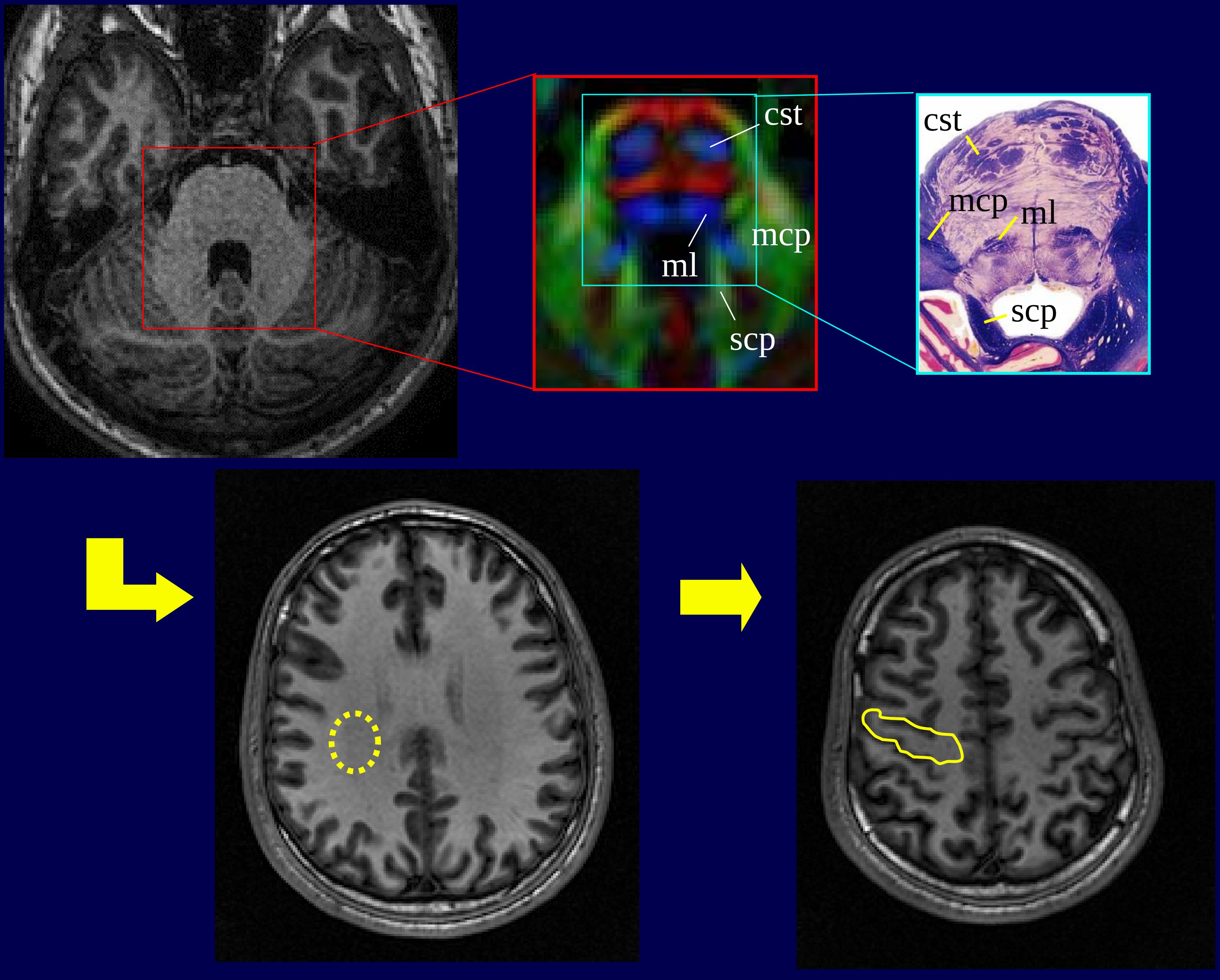
Axonal projection reconstruction may be possible

ROI placement decides specificity of tractography

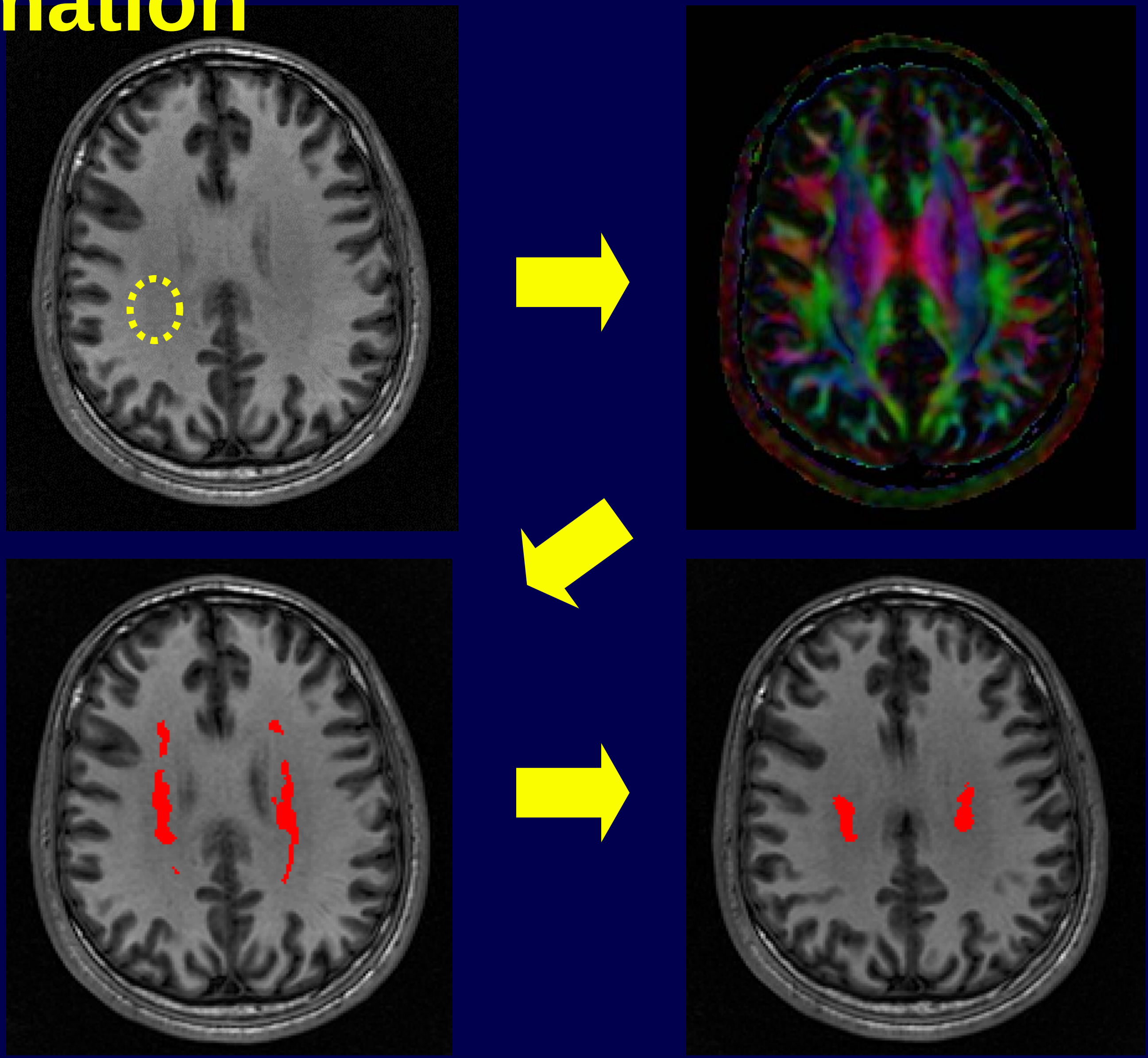


Comparison with postmortem samples

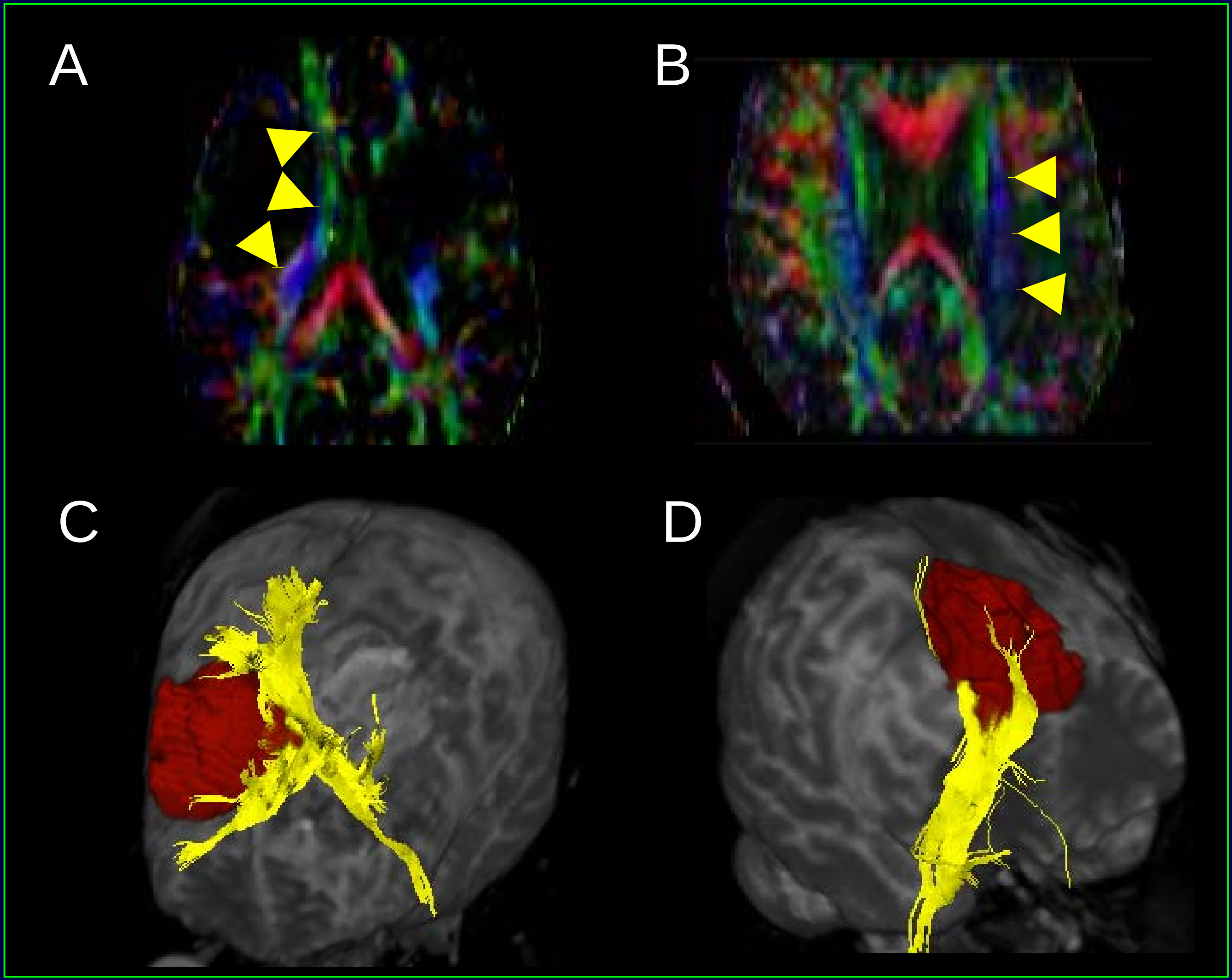


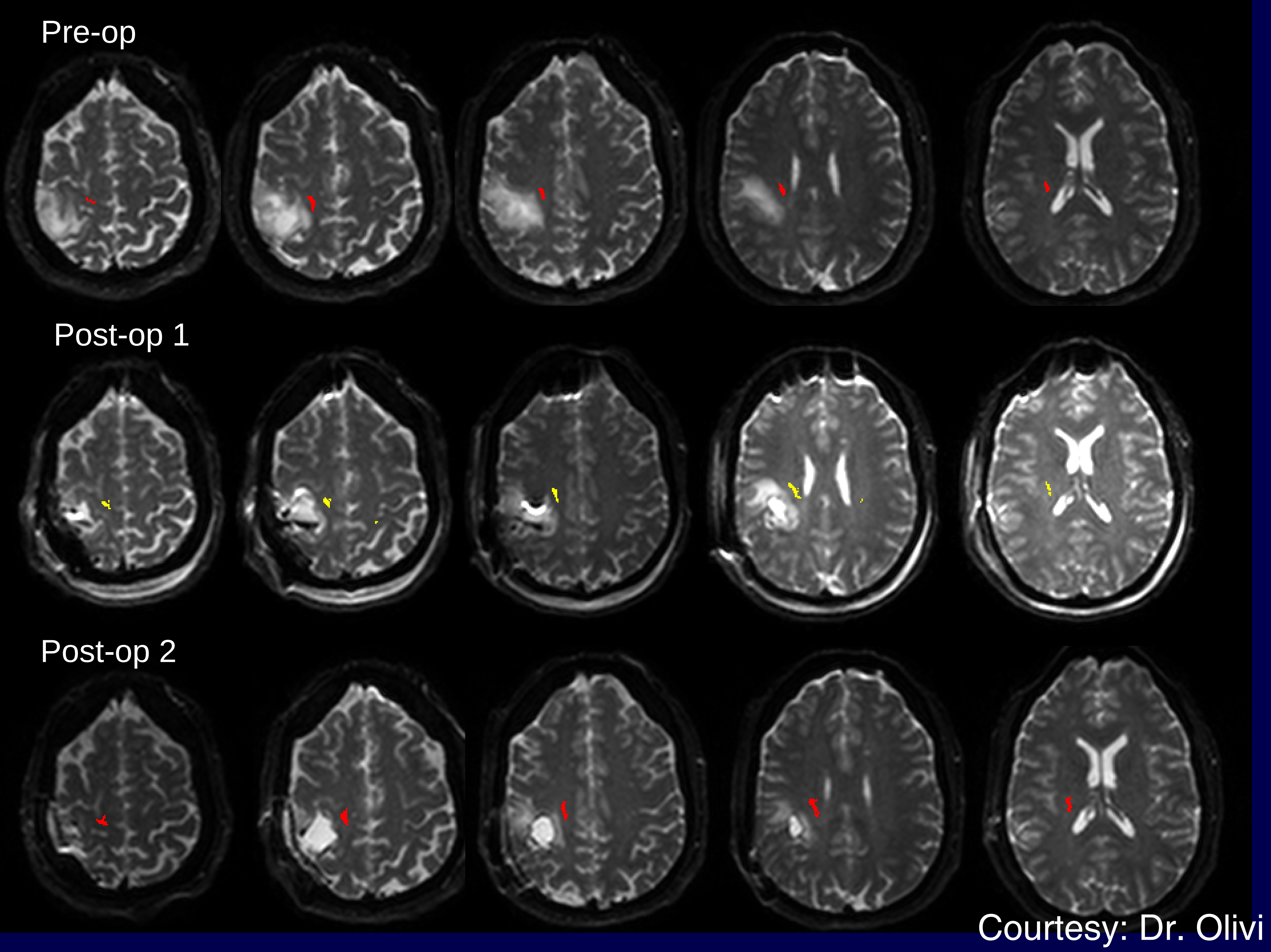

cst
mcp
ml
scp
cst
mcp
ml
scp

Refinement of CST location using DTI information



DTI of tumor patients





Pre-op
Post-op 1
Post-op 2
Courtesy: Dr. Olivi

Content

- Principle of DTI
- Principle of tractography
- Application to brain tumor surgery
  - How real? Validation
  - False positive / negative?
  - Efficacy?

Acknowledgement

Hangy Jiang: Data Processing

Peter van Zijl: Human data

Alessandro Olivi: Tumor study

Setsu Wakana / Lidia Poetscher: Human data

Philips Medical System

New MRI Technologies with Clinical Potential

Peter van Zijl
Professor of Radiology, Johns Hopkins University
Director, F.M. Kirby Research Center for Functional Brain Imaging
Kennedy Krieger Research Institute

Presentation by: Manus J. Donahue

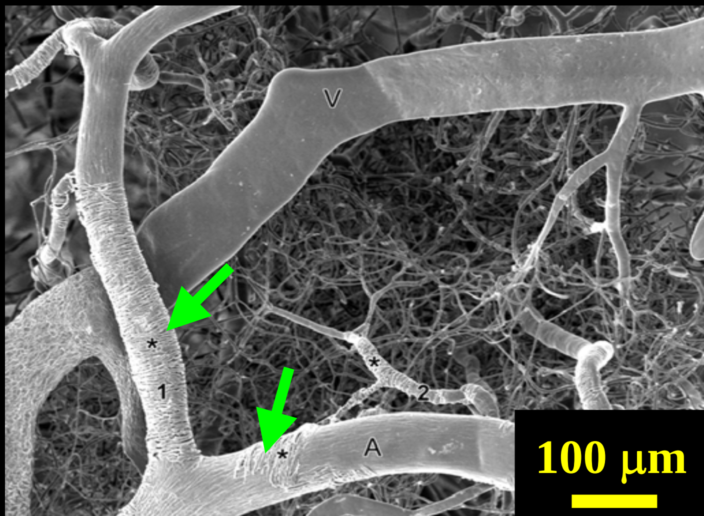
Kennedy Krieger Institute

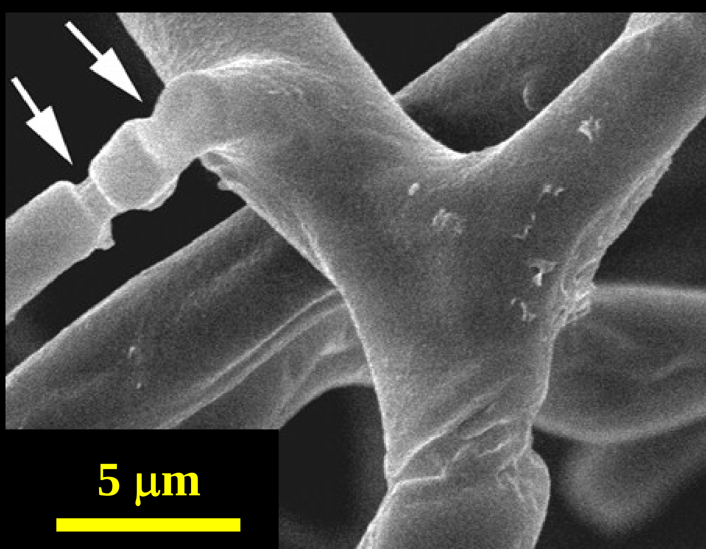
NCRR

F.M. Kirby Research Center for Functional Brain Imaging

JOHNS HOPKINS MEDICINE

Arterioles and Capillaries Contain Complex Flow Control Structures





Smooth muscle surrounds arterioles

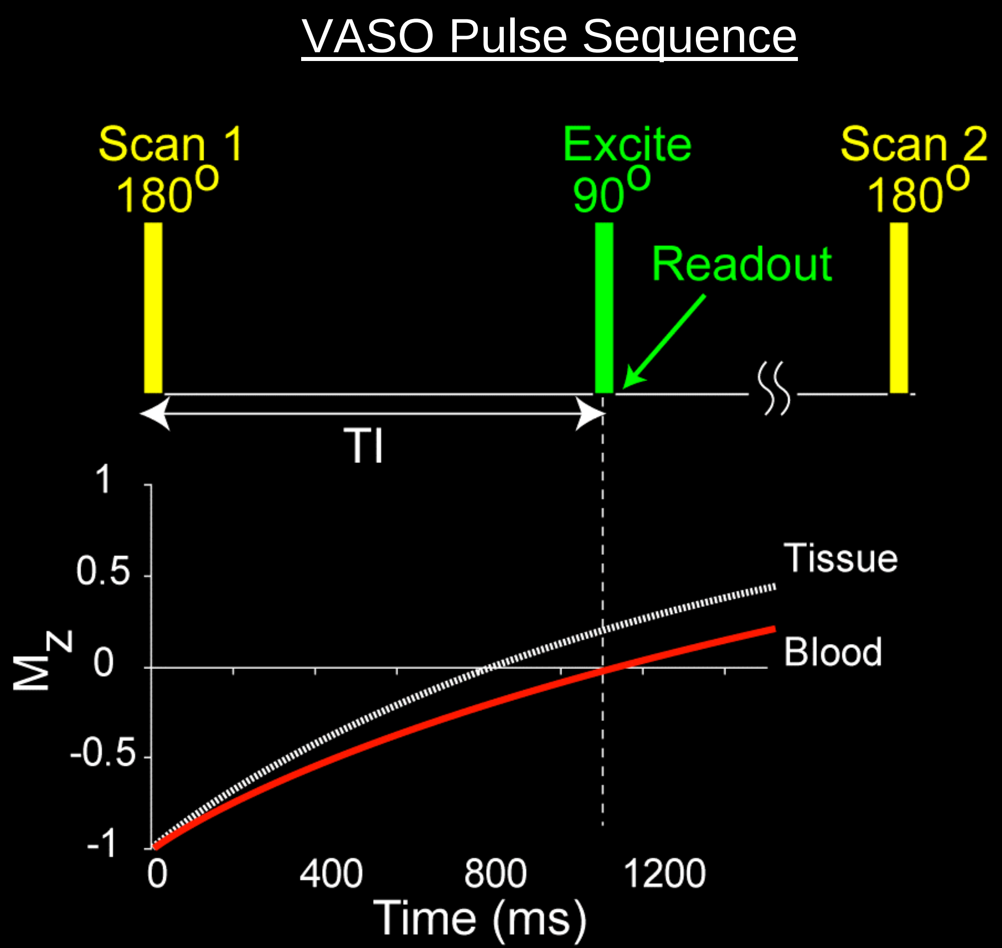
- Facilitates changes in arteriole diameter

Pericytes containing contractile proteins line capillaries

- Regulates capillary diameter

Images from: Harrison, et al. *Cerebral Cortex*. **12.** 2002.

Image Cerebral Blood Volume (CBV) Changes with T1-weighted Vascular-Space-Occupancy (VASO) MRI



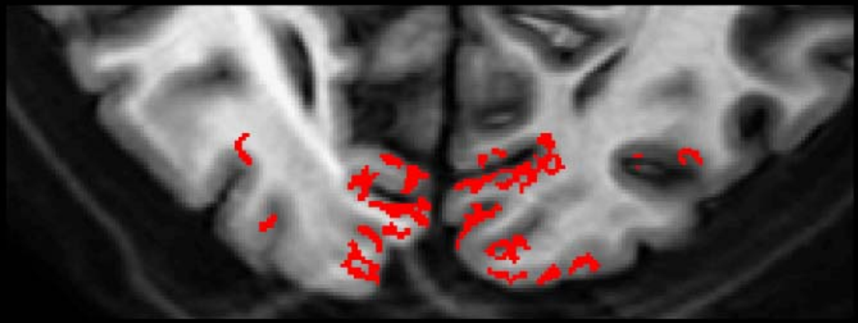
Blood water protons and tissue water protons behave differently in the presence of a magnetic field

VASO Principle: Acquire an image when intravascular blood signal is zero, yet tissue signal is positive

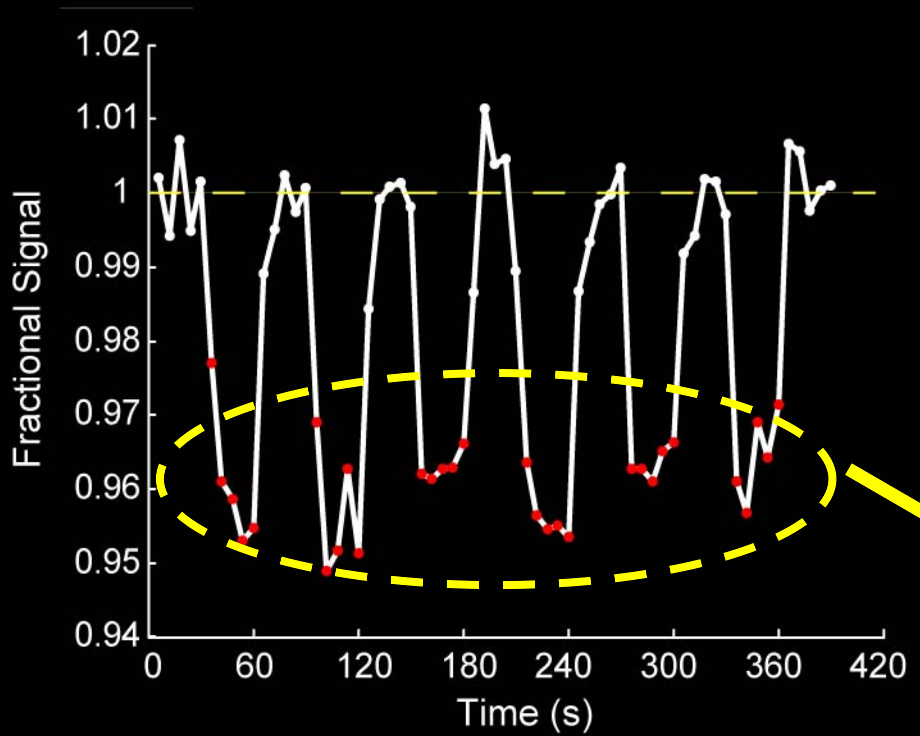
Dark areas in VASO image reflect high CBV; bright areas reflect lower CBV

Lu H, et al. *Magn Reson Med.* 2003.

VASO Identifies CBV Increases Associated with Brain Activation



Visual stimulation
activation map



VASO signal intensity decreases during activation

Signal decrease (4-5 %) due to vasodilation

VASO MRI has become popular for studying brain activation in healthy subjects

1. **Retinotopic Mapping**: Lu, H et al. Neuroreport. 2005;16(15)
2. **Contrast Mechanisms**: Donahue, MJ et al. Magn Reson Med. 2006; 56(6)
3. **Sequence Improvements**: Poser, BA et al. MAGMA. 2007;63-7. Epub 2007

Many pathologies associated with changes in CBV, hemodynamic reactivity and vessel compliance

Is VASO useful in the clinic?

Apply VASO to patients with gliomas

VASO May be Important for Segmenting High-grade Gliomas

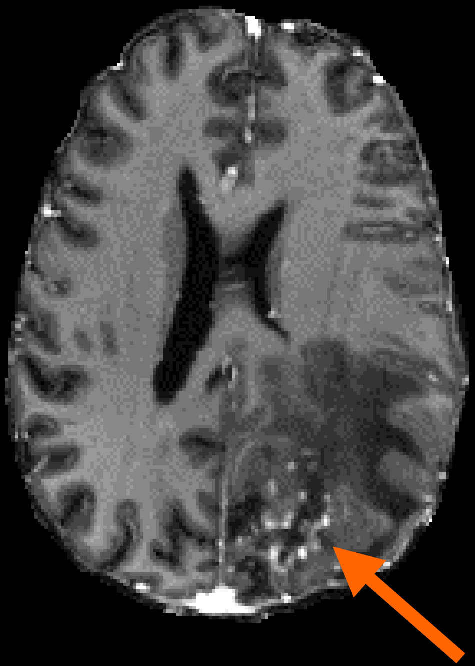
- Prognosis for patients with high-grade gliomas is poor. Median survival time without treatment is 3 months.

- Therapy and surgical resection can extend median survival time to > 1 year (Mason et al. *N Engl J Med* **352**)

- Problem: gliomas are very heterogeneous and infiltrative. What is healthy tissue, active tumor, necrosis or edema?

- *What should be cut or treated?*

Currently, Resection Based Largely on GAD Enhancement in T1w Images



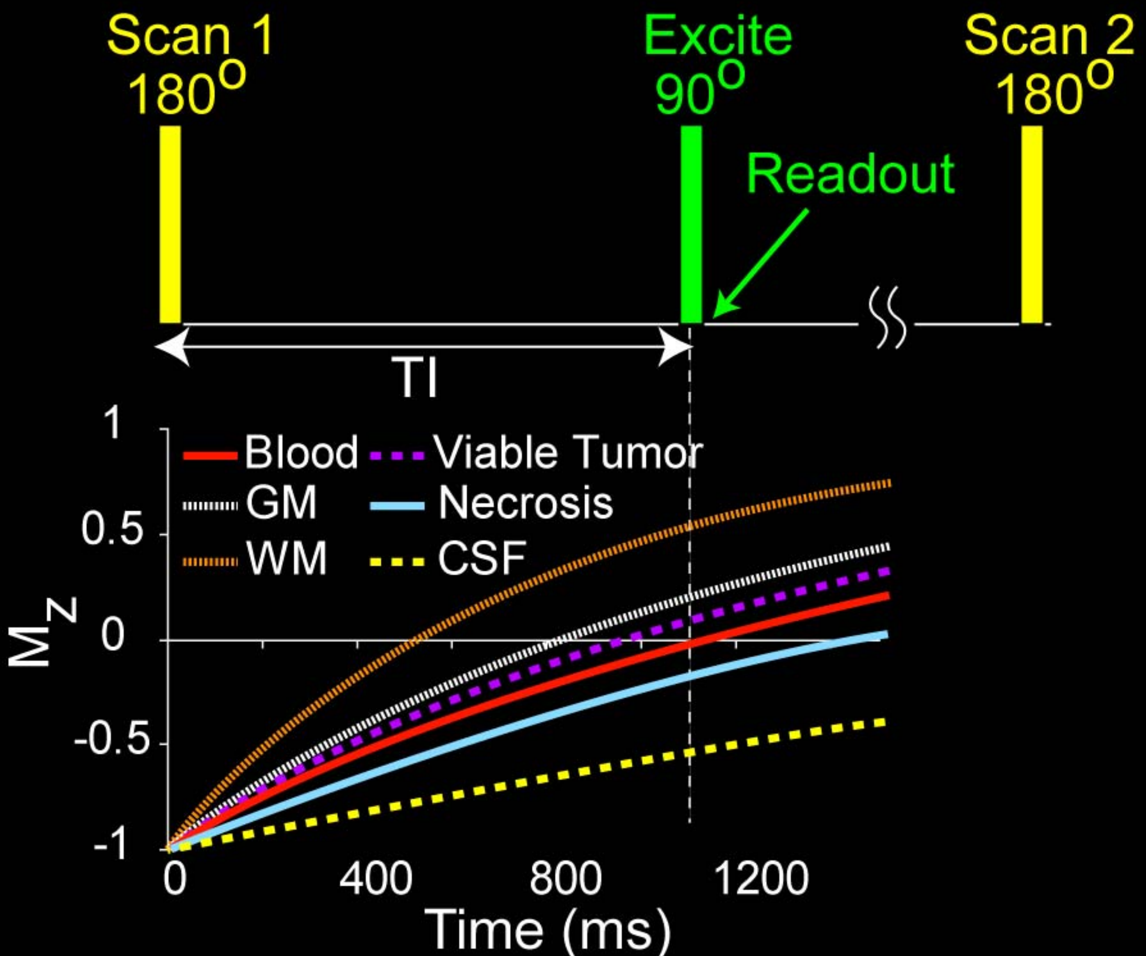
GAD-T1w MRI

1. Inject contrast agent (GAD)
2. Acquire T1-weighted image
3. Enhancement in region of blood-brain barrier breakdown (active tumor)

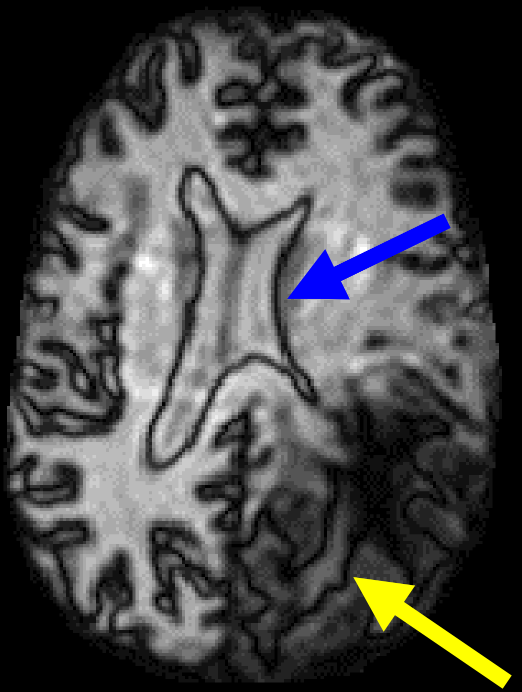
Problems:

1. Invasive
2. Enhancement difficult to see
3. Some high-grade gliomas do not enhance
4. Some low grade gliomas do enhance

Different Tumor Components have Different T1



Anaplastic astrocytoma



VASO Image

Experimental Setup

Scan ten patients with histologically-confirmed gliomas:

Four gliobastoma multiforme (GBM)
Two anaplastic astrocytoma (AA)
One anaplastic oligodendroglioma (AO)
Three low-grade (LG)

T1-weighted MRI Scans:

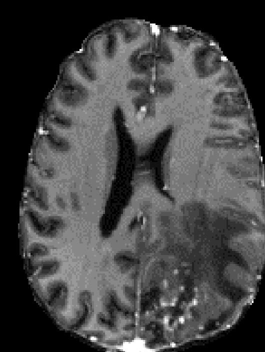
FLAIR

tumor;
edema

MPRAGE

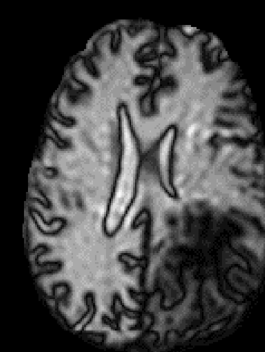
T1 zones

T1w+GAD

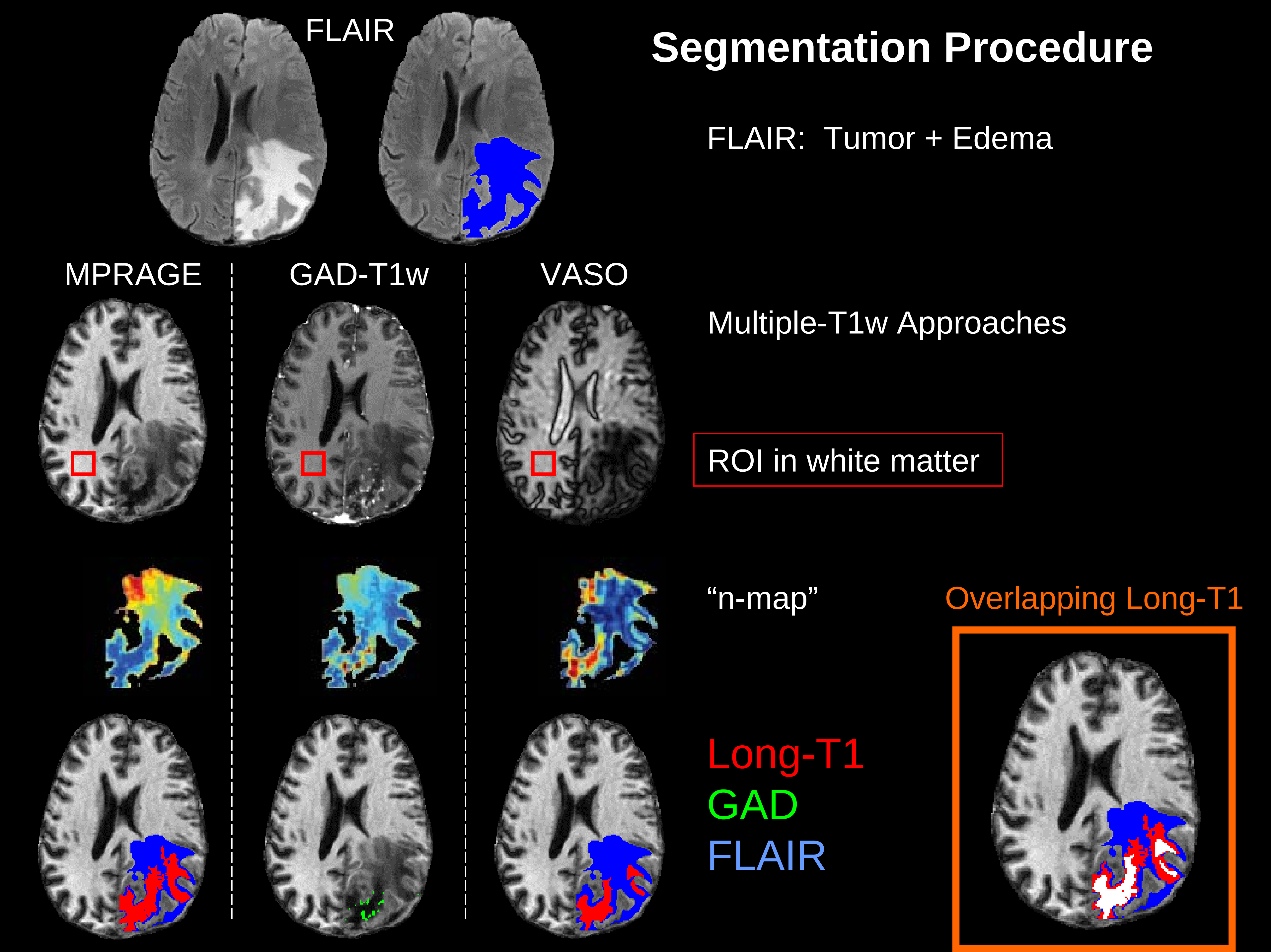


BBB breakdown

VASO

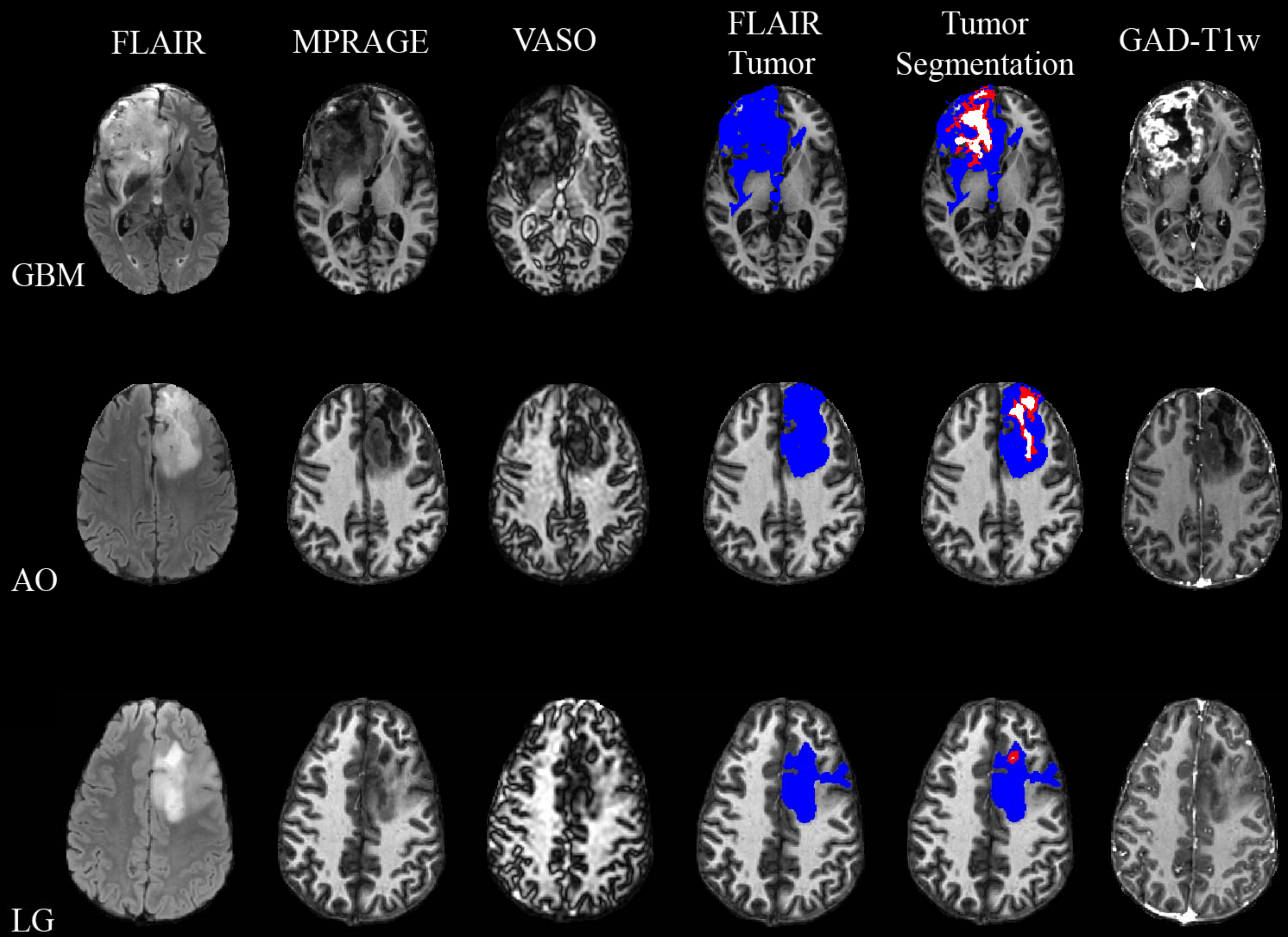


T1 zones;
CBV



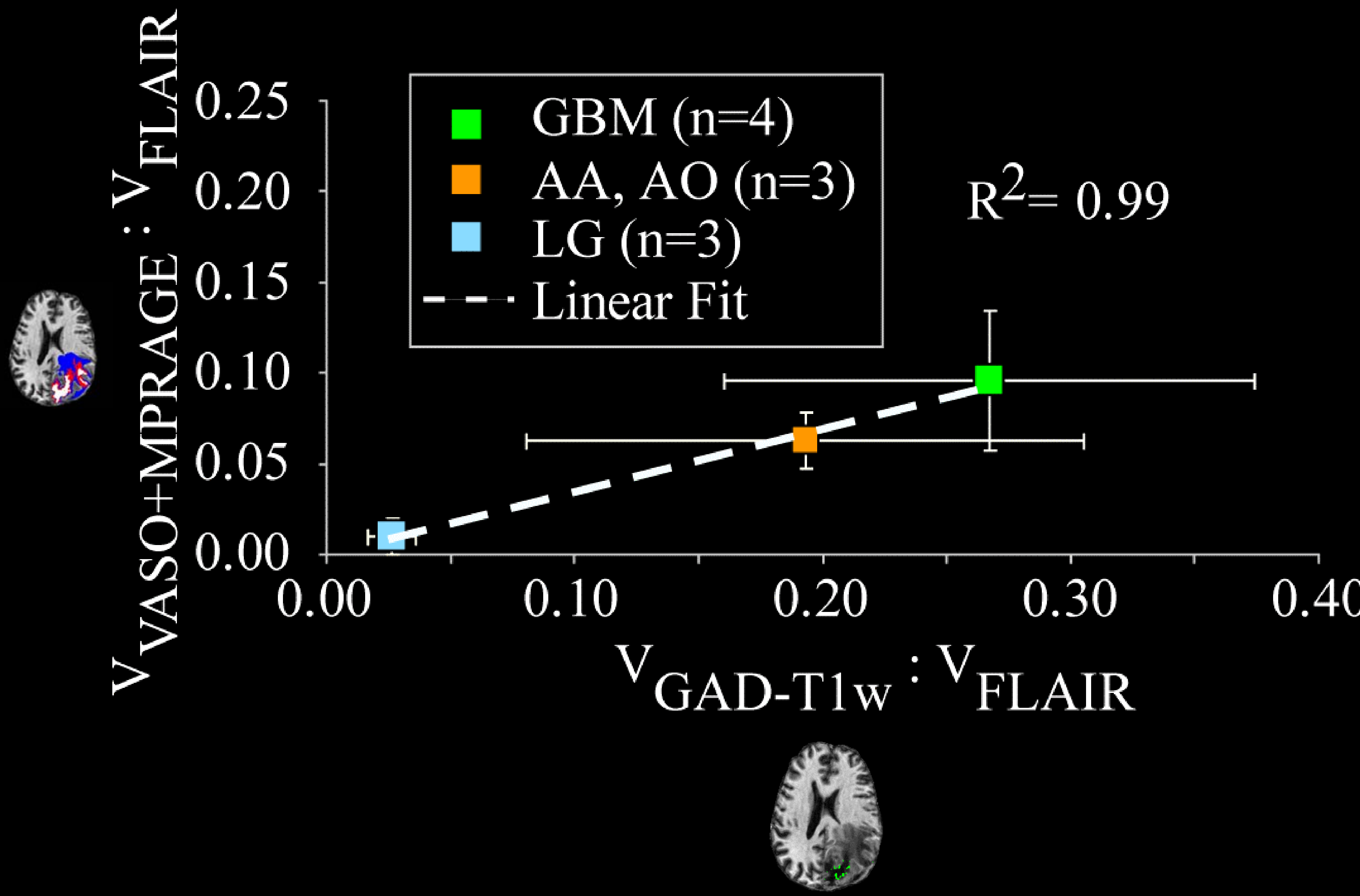
Segmentation Procedure
FLAIR
FLAIR: Tumor + Edema
MPRAGE
GAD-T1w
VASO
Multiple-T1w Approaches
ROI in white matter
"n-map"
Overlapping Long-T1
Long-T1
GAD
FLAIR

Tumor Segmentation Using Multiple T1w Approaches

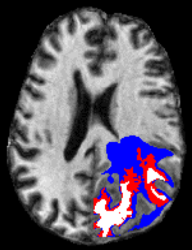


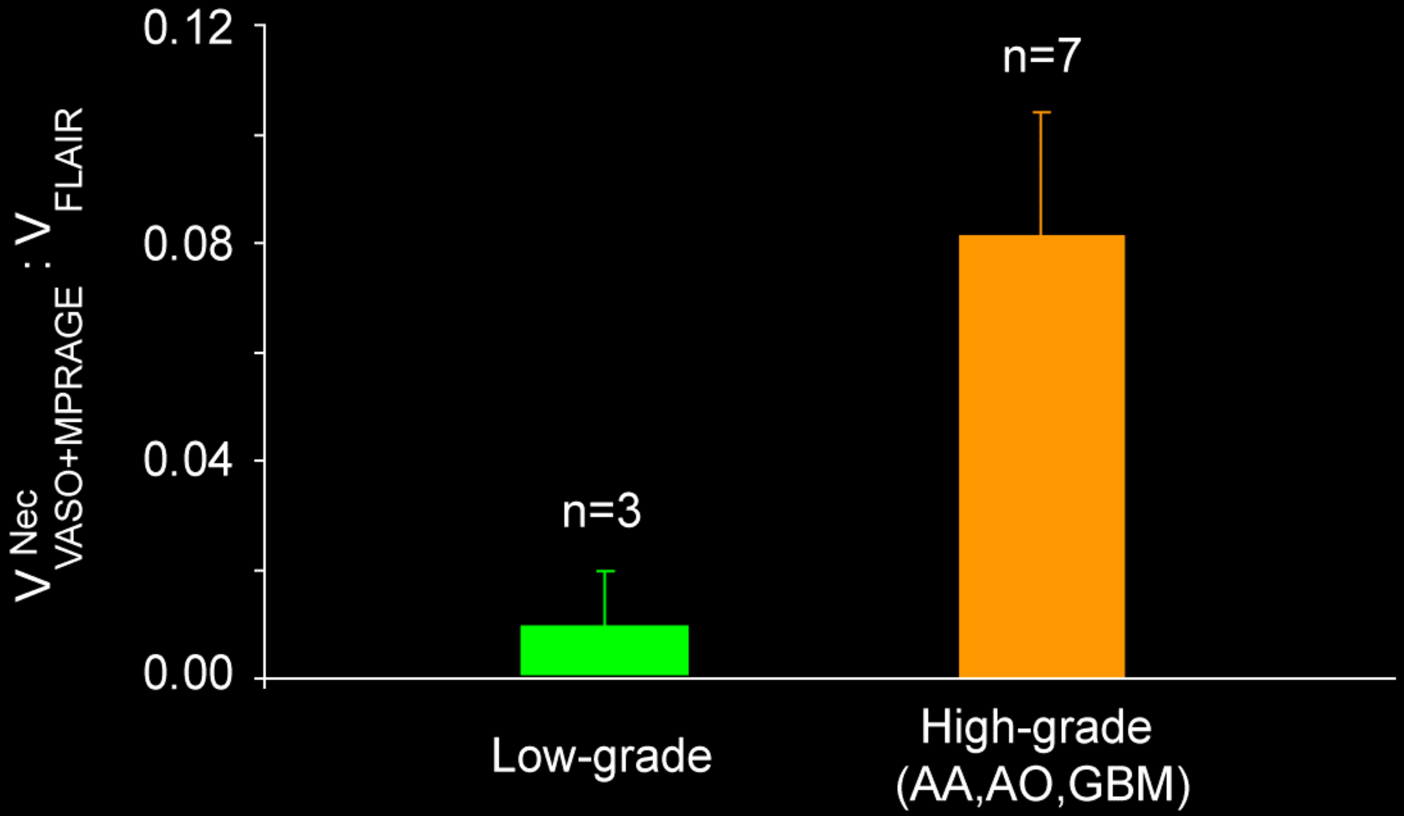
GBM: Glioblastoma multiforme; AO: Anaplastic oligodendroglioma; LG: Low-grade

Long T1 Region Correlates with GAD Enhancement

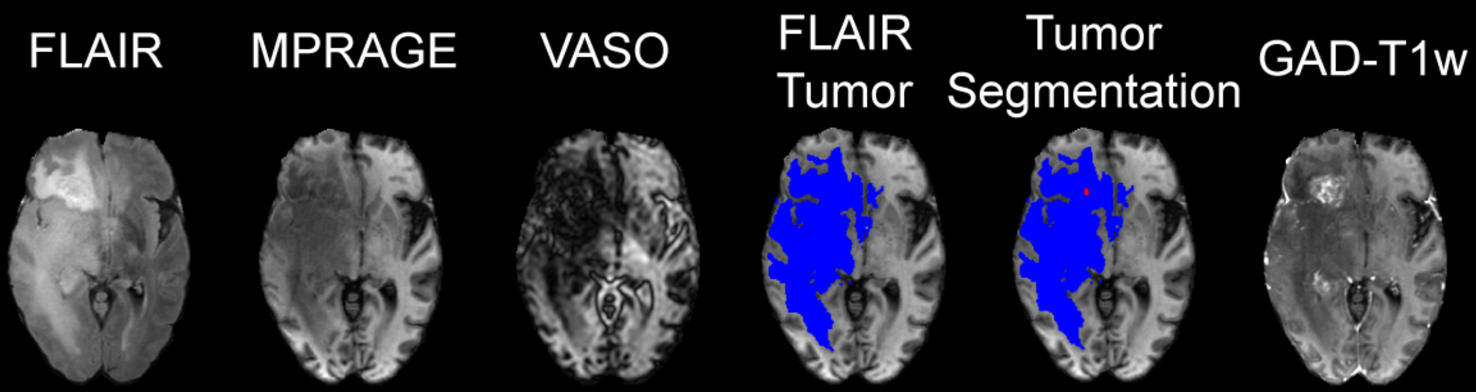


Long T1 Region Correlates with Tumor Grade





Biopsy-confirmed Low-grade with Treatment Effect



No predicted long T1 zone; suggests low-grade diagnosis

Combined MPRAGE and VASO approach may be useful for distinguishing treatment effect from necrosis associated with progressive tumor

Conclusions

Multiple T1-weighted MRI approaches were combined to noninvasively segment gliomas into separate regions

VASO provided novel information due to the black borderline which surrounded the predicted necrotic zone

The presence of a necrotic region correlated with tumor grade and the volume of enhancement in GAD-enhanced MRI.

Future applications of VASO

Track antiangiogenesis therapy

Measure CBV reactivity in different tumor zones

Apply to other diseases of the central nervous system
(currently: ischemic stroke, carotid artery steno-occlusive disease)

Acknowledgements

Patients

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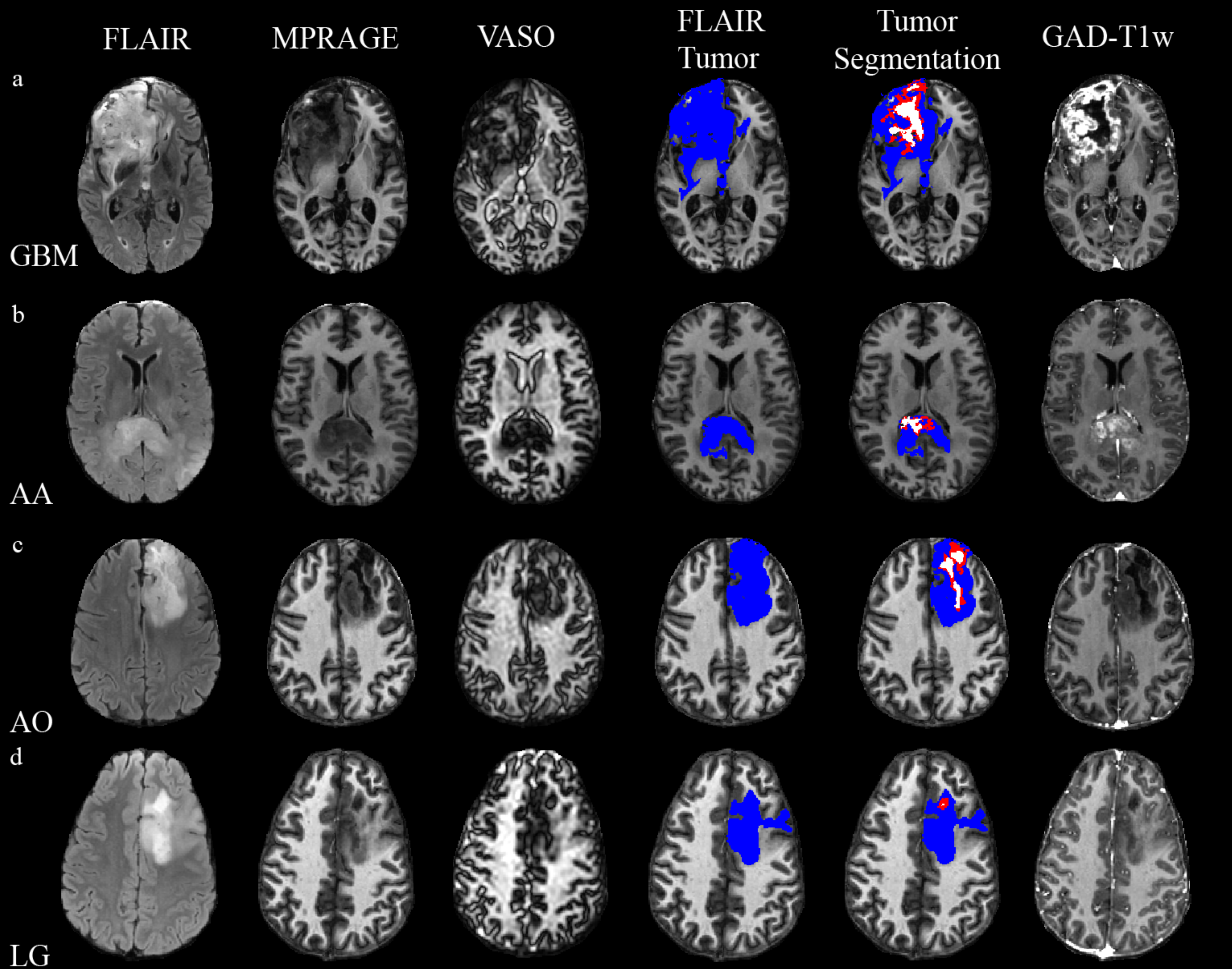
NIH-NIBIB EB002666


FLAIR
MPRAGE
VASO
FLAIR Tumor
Tumor Segmentation
GAD-T1w
a
GBM
b
AA
c
AO
d
LG

APPLICATION OF HIGH RESOLUTION STRUCTURAL IMAGING TO BRAIN DEVELOPMENT

Barry E. Kosofsky, M.D., Ph.D.

Some Slides Adapted From
P. Ellen Grant, M.D., MGH
Pierre Gressens, M.D., Ph.D., INSERM

New Advances in Structural and Functional Brain Imaging

- With new brain imaging tools we can for the first time “see” human brain activity in infants and children
- Such advances permit us to look at normal brain development and disease-induced changes
- These approaches will improve our diagnostic and therapeutic abilities

Imaging The Newborn (and Acutely Injured) Brain

- A significant number of newborns suffer brain damage around the time of birth
- The consequences of such injury can result in life-long compromise
- In some cases the damage may be preventable or minimized. As in adults, this requires immediate recognition and treatment:
  – Goal: Diagnose and Treat "Brain Attacks"

Hurdles- Dx/Rx
"Brain Attacks"

- Brain injured infants and children may be "unstable", so the requisite technology should be readily available
- Need for information regarding the normal range of brain activity (at rest and with noise or light stimulation)
- Identify "markers" predictive of trouble
- Identify therapy to prevent more trouble

‘ Brain Attacks ’

Toxic Factors

hypoxia-ischemia
maternal infection
stress
thyroid deficiency
genetic factors

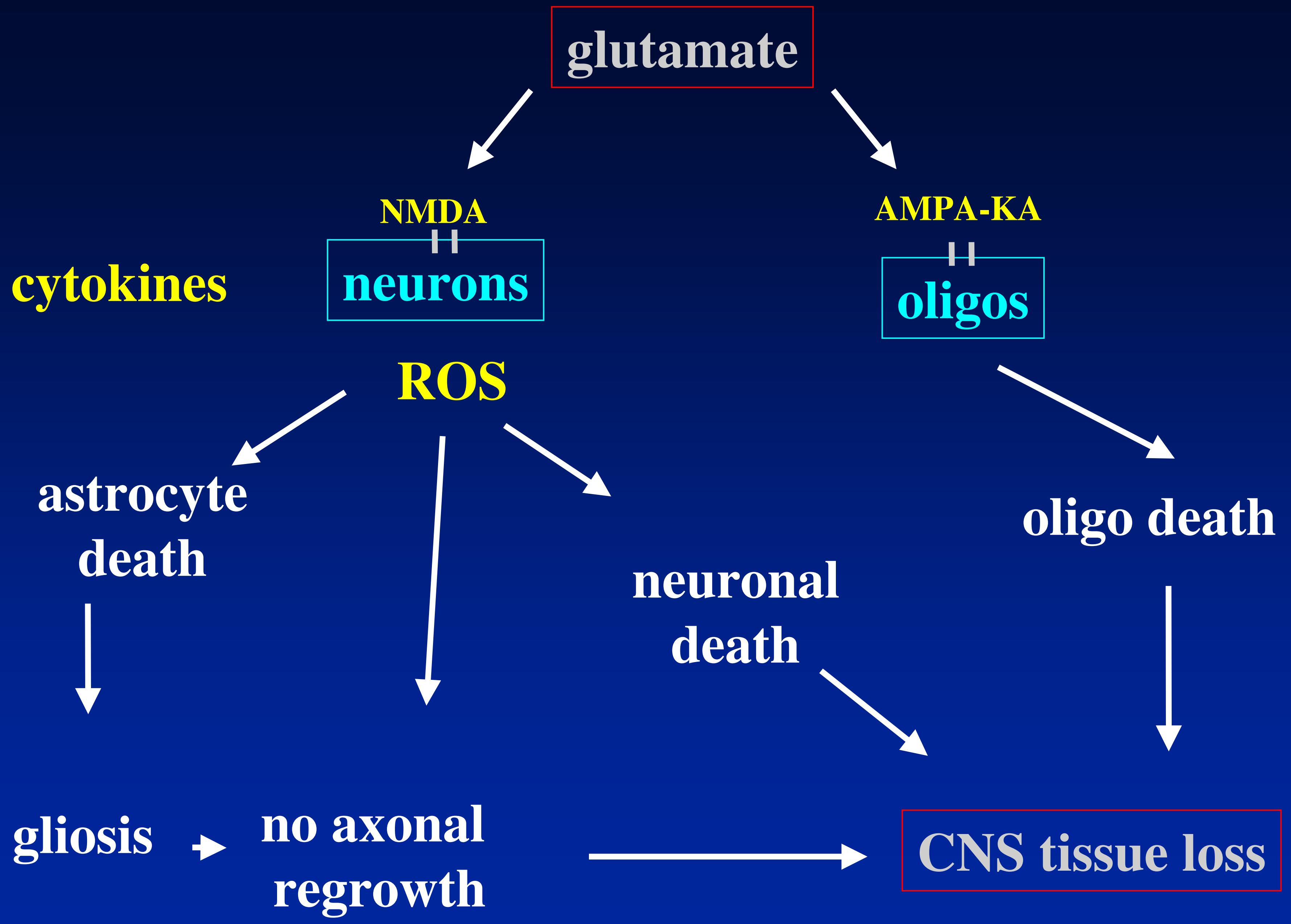
Protecting Factors

growth/trophic factors
free radicals scavengers

$\boxed{\textbf{Excitatory Amino Acids}}$

⬇

Brain Damage


glutamate
NMDA
AMPA-KA
cytokines
neurons
oligos
ROS
astrocyte death
neuronal death
oligo death
gliosis
no axonal regrowth
CNS tissue loss

We Can Assess Physiology Non-invasively with Functional Brain Imaging

<u>Hemodynamic</u>
- Oxy- & Deoxy-Hemoglobin
- Blood Volume
- Blood Flow

<u>Neuronal - Electrical</u>
- Voltage sensitive dyes
- Calcium Green
- Scattering

<u>Metabolic</u>
- Cytochrome oxidase
- NADH - FADH

Diffusion

Diffusion

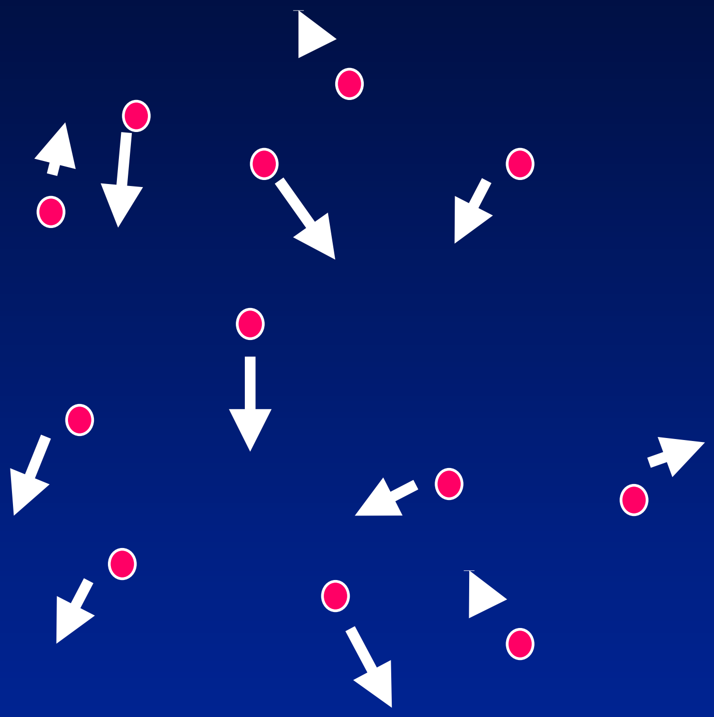
- Small random motion of water due to its kinetic energy and molecular collisions

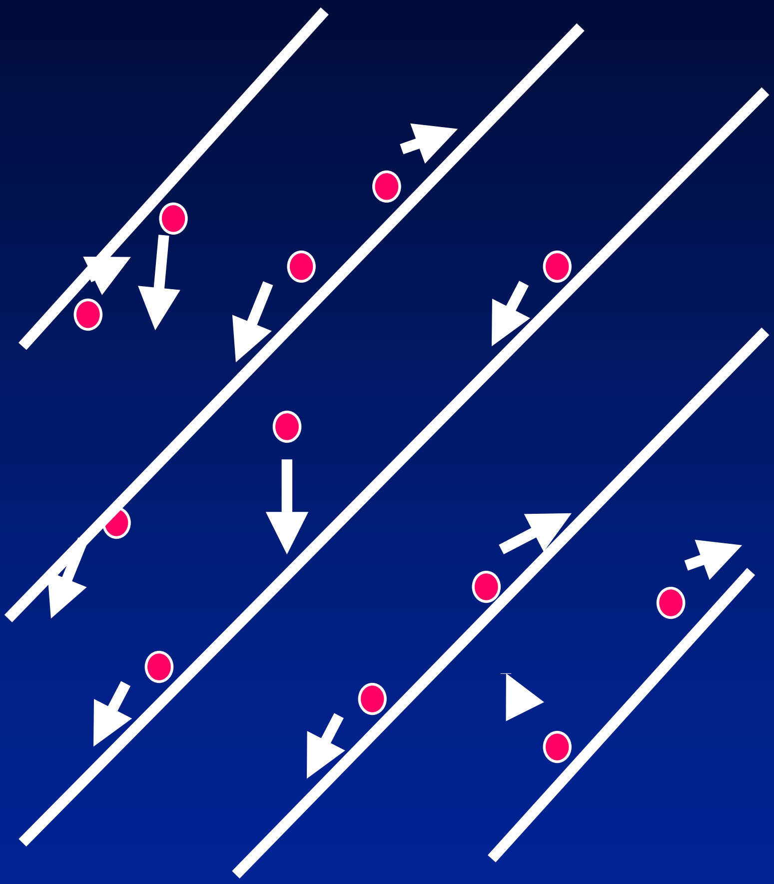
Apparent Diffusion

- Motion of a molecule due to diffusion + bulk flow

Cannot separate motion due to bulk flow from motion due to only to Diffusion therefore measure Apparent Diffusion

Diffusion

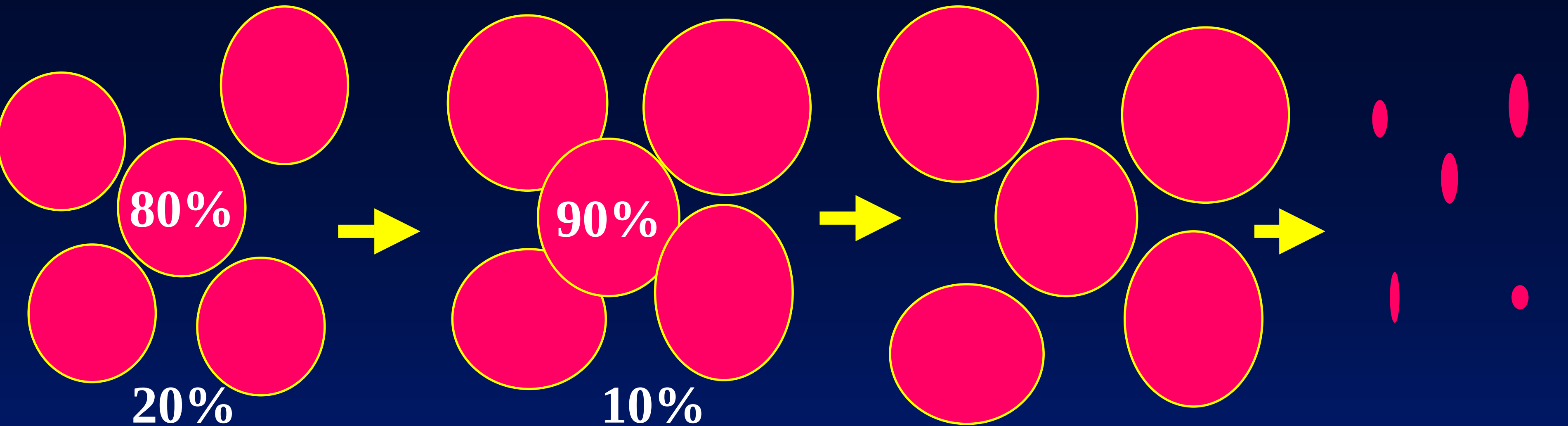




isotropic

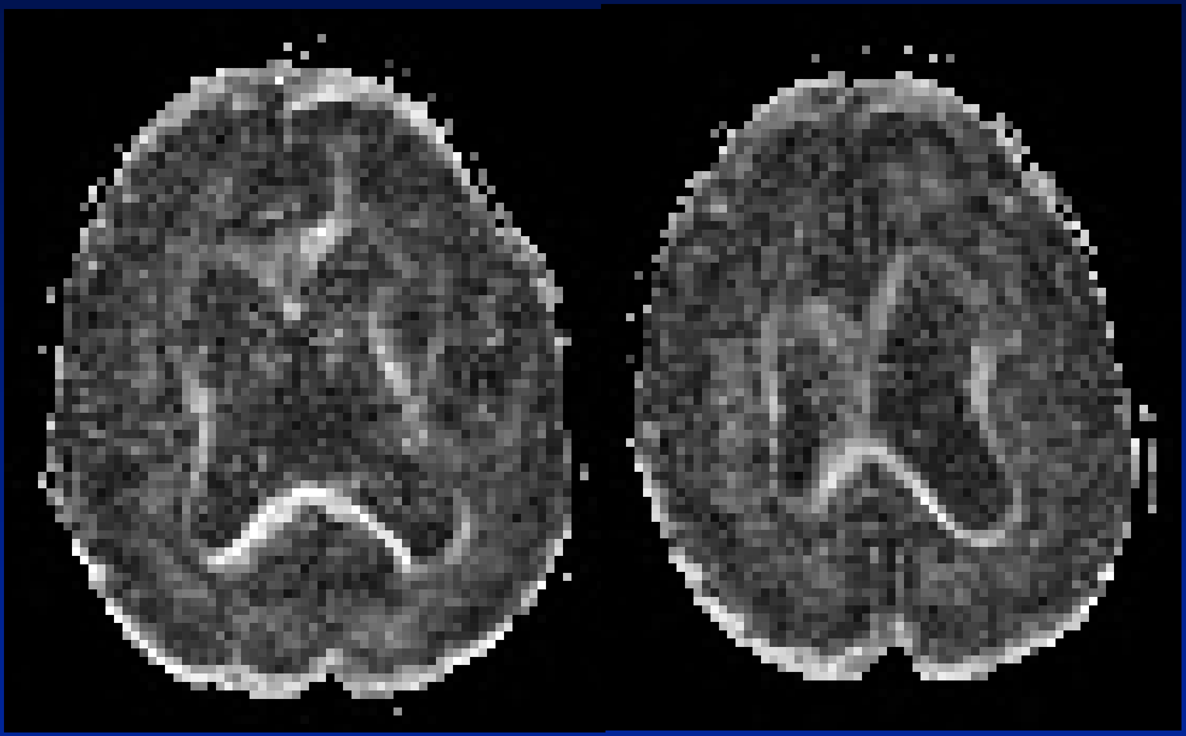
anisotropic

Fractional Anisotropy

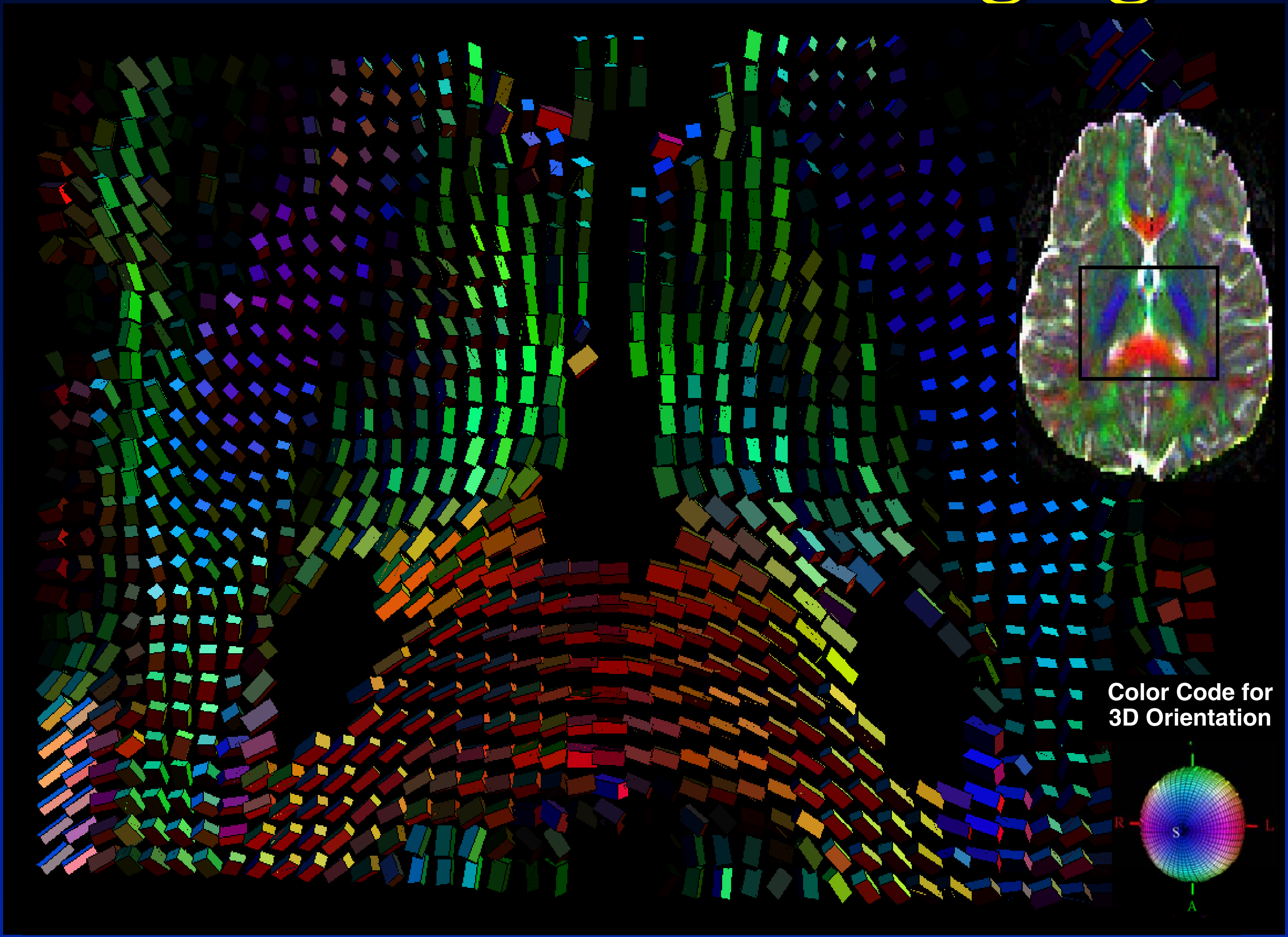


Healthy	Na-K Pump Dysfunction / Hyperacute Cellular Necrosis	Acute/Subacute Cellular Necrosis	Atrophy
ADC	↓	↓	↑
T2	↔	↑	↑

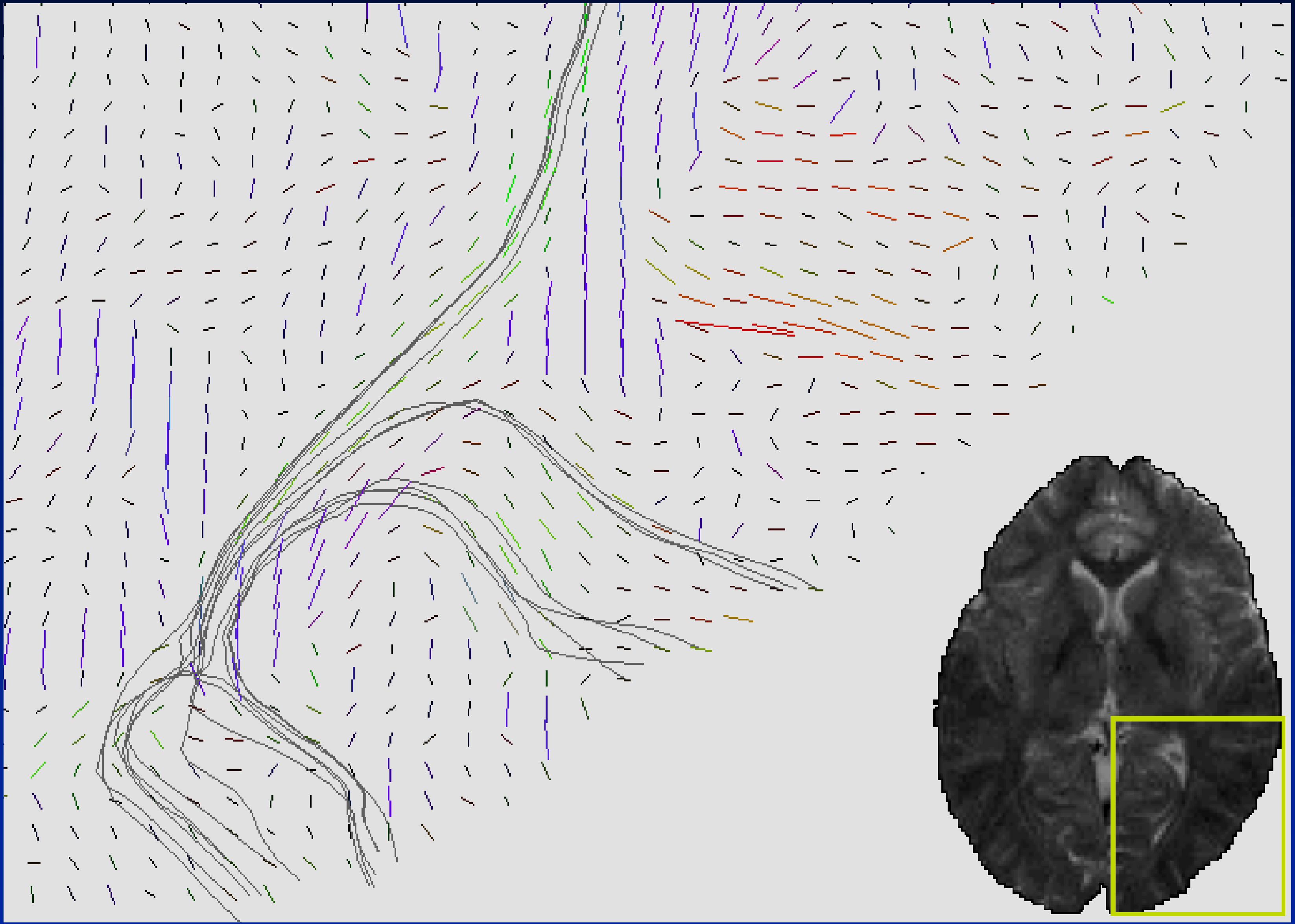
Fractional Anisotropy



Diffusion Tensor Imaging



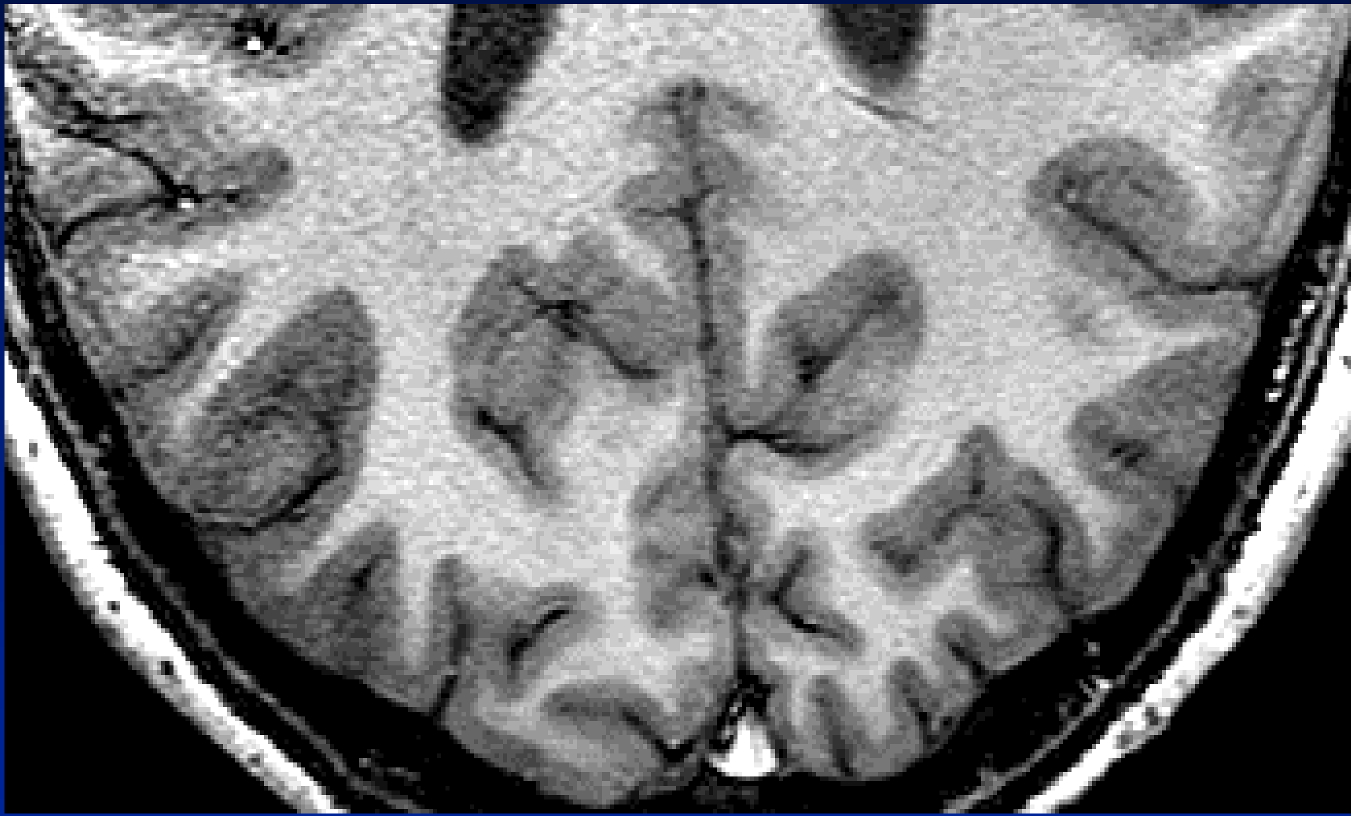
Tractography: A Materials-Based Approach



Wedeen, Tuch, Reese

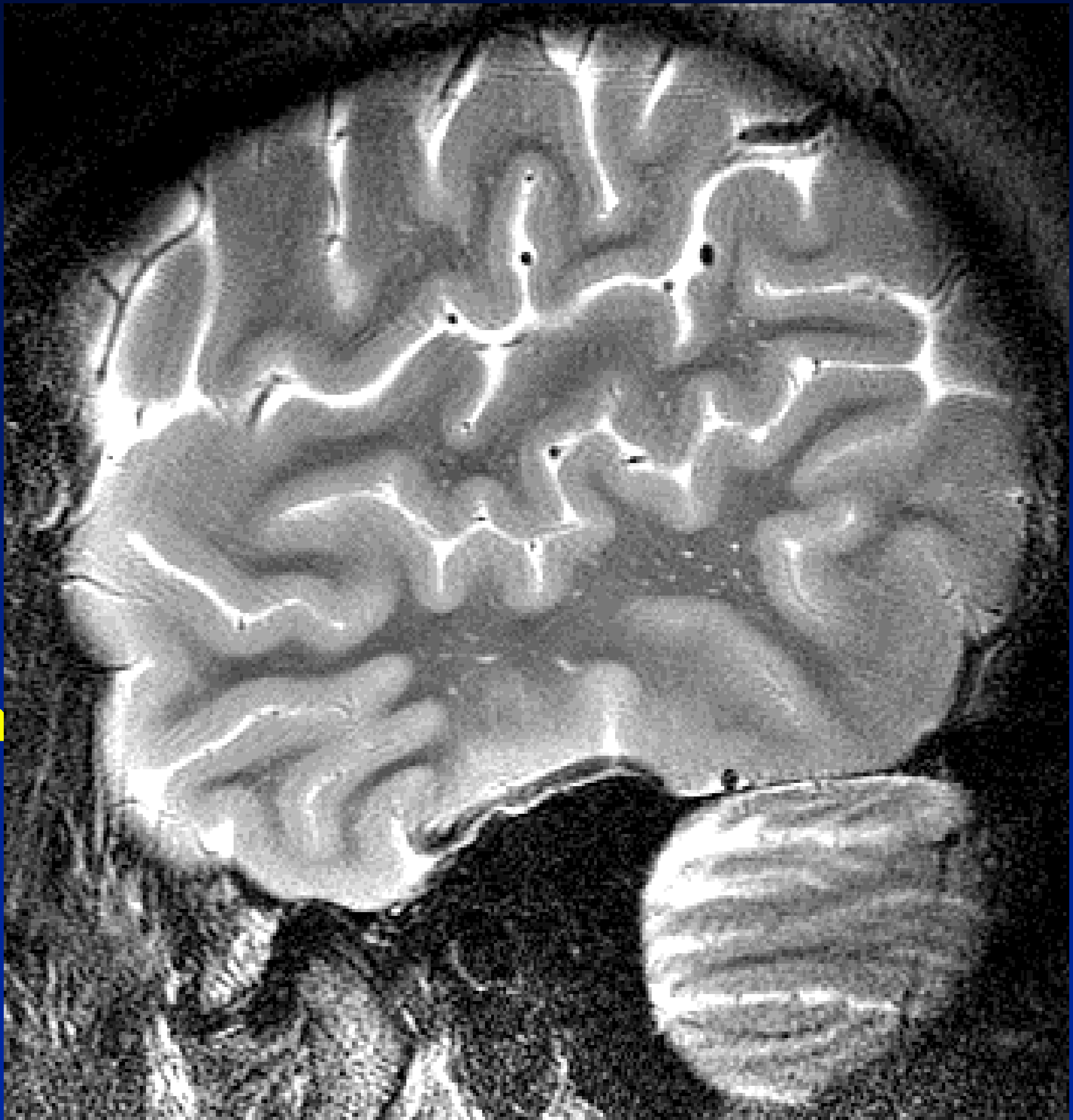
Receive-only surface coil at 3T

IR- 3D SPGR
TR/TE/flip =
20 / 4.6 / 25 deg.
TI = 300ms
16 kHz BW
4:59 min. scan time
512 x 256
20 cm x 15cm FOV
1.5 mm partition
390 um x 586um x 1.5mm
= 0.34 mm^3



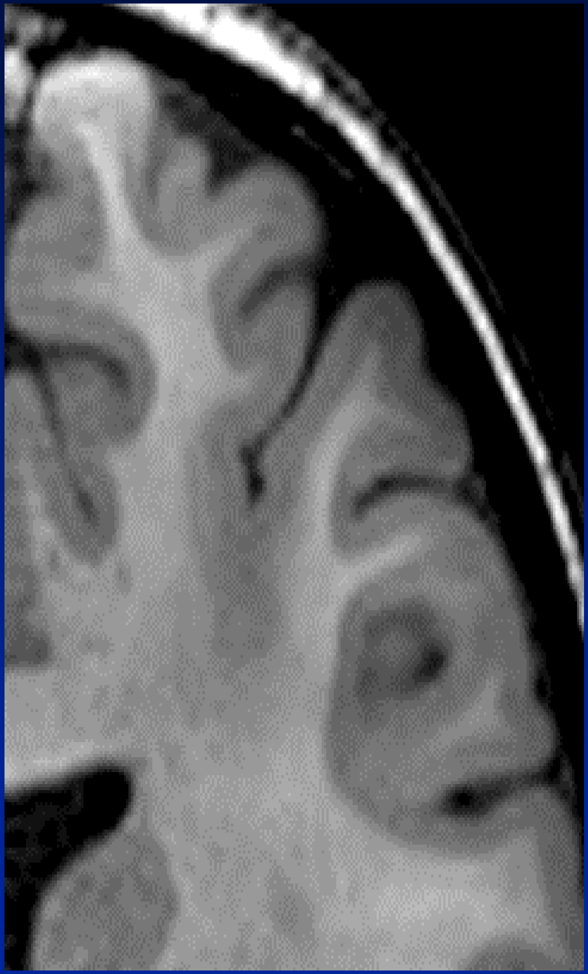
Receive-only surface coil at 3T

2D FSE
TR/TE= 4000/ 102
32 kHz BW
ETL = 8
512 x 384
16cm x 16cm FOV
3mm slice
313 um x 417 um x 3n
= 0.39 mm^3



MRI and Neuroanatomy

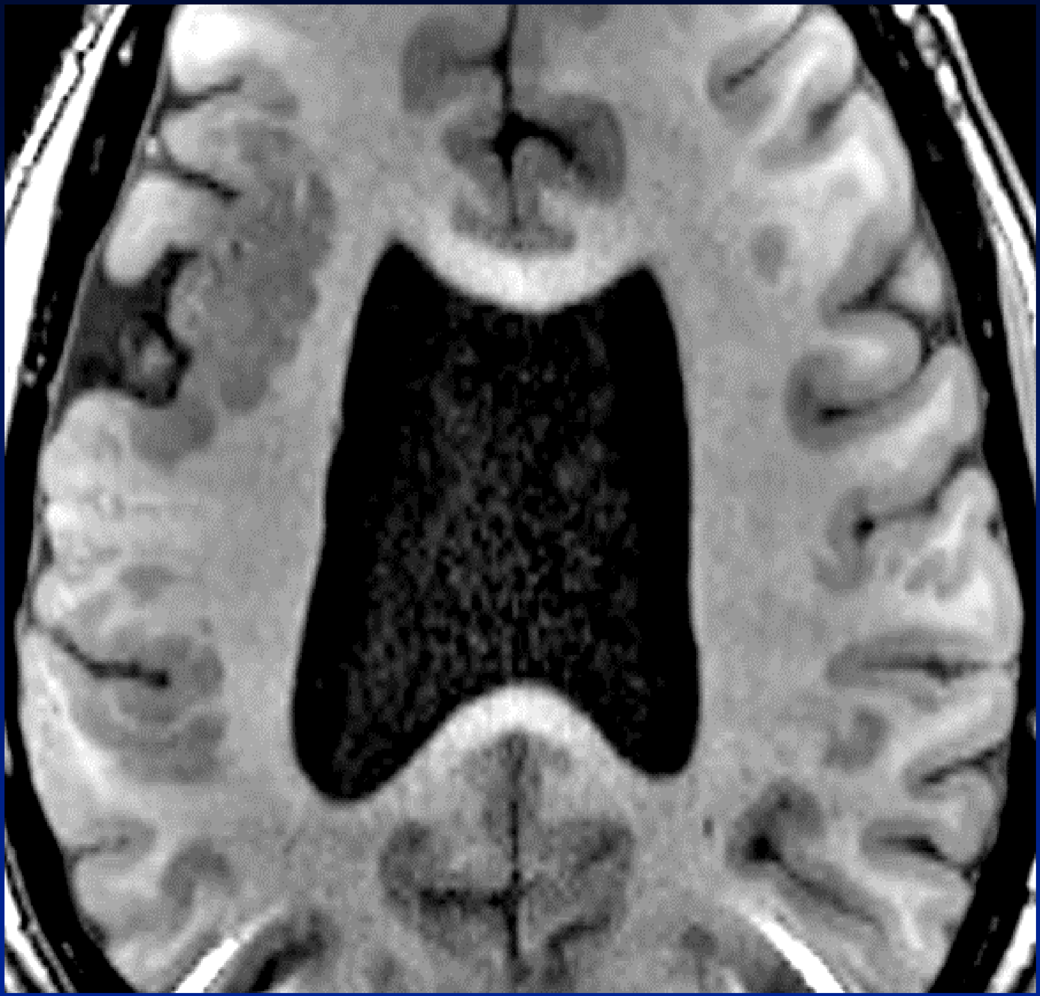
T1



T2

Transmantal Dysplasia

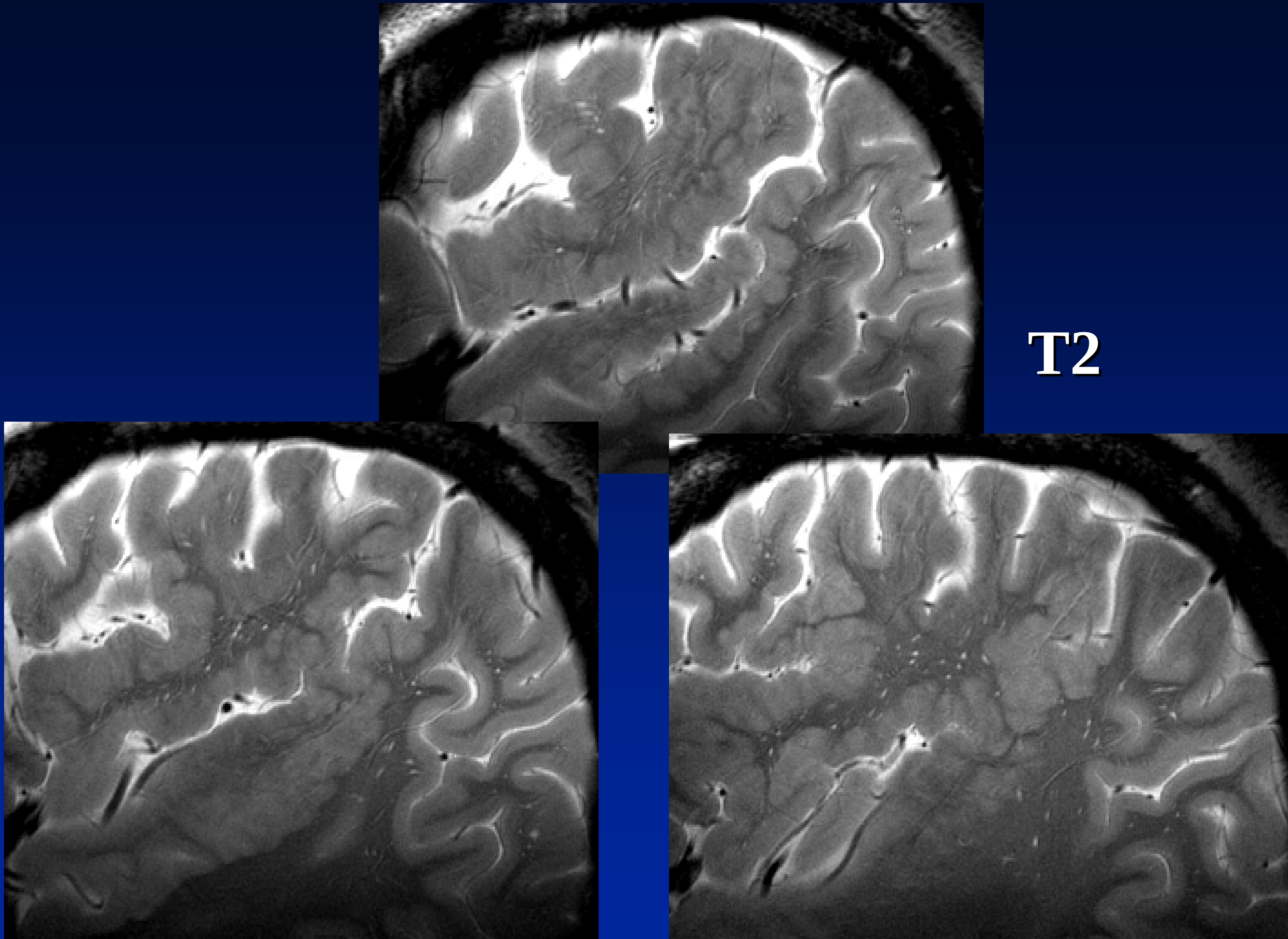
Grant, Wald



T1

Polymicrogyria (PMG)

Grant, Wald



T2

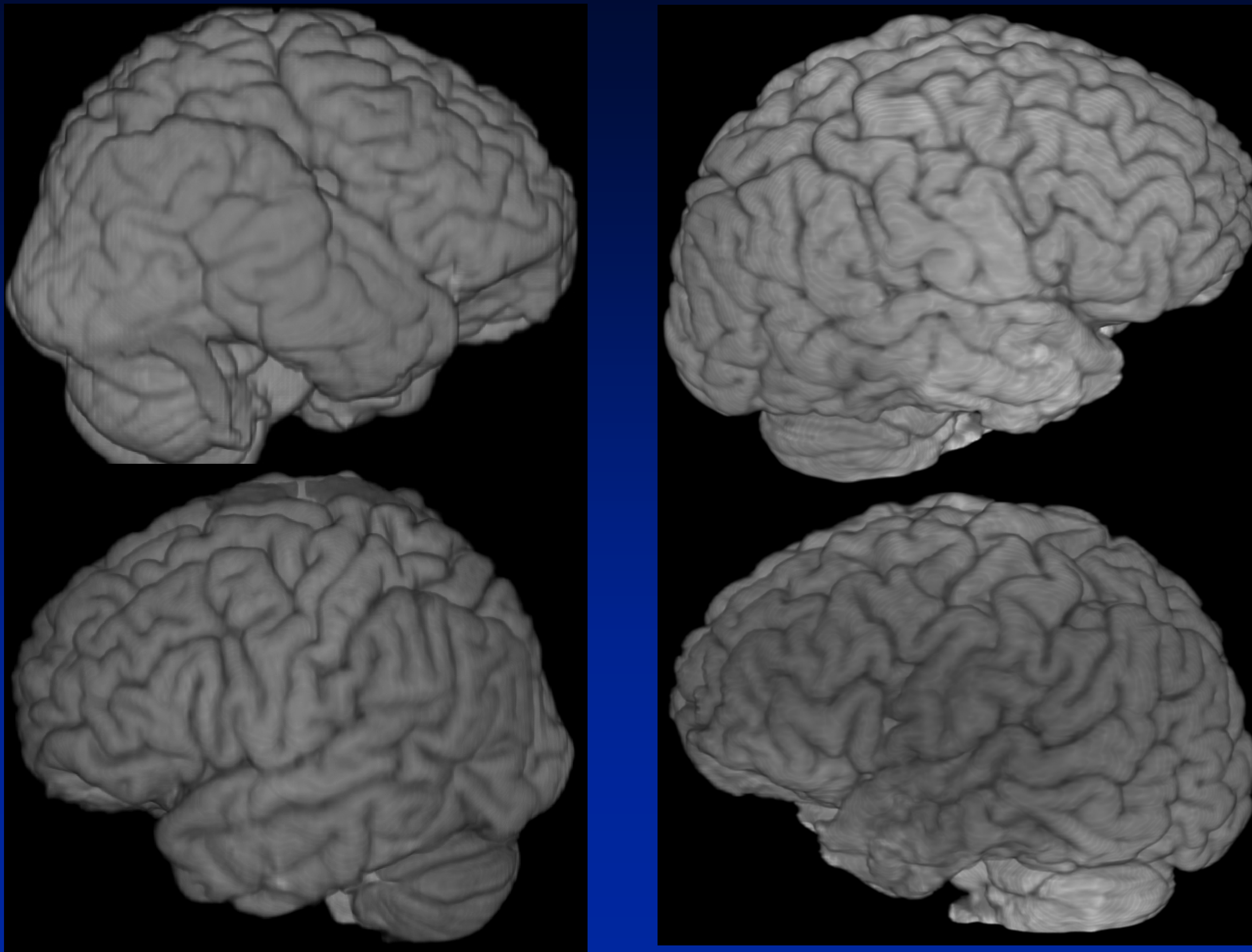
Polymicrogyria (PMG)

Grant, Wald

PMG Normal

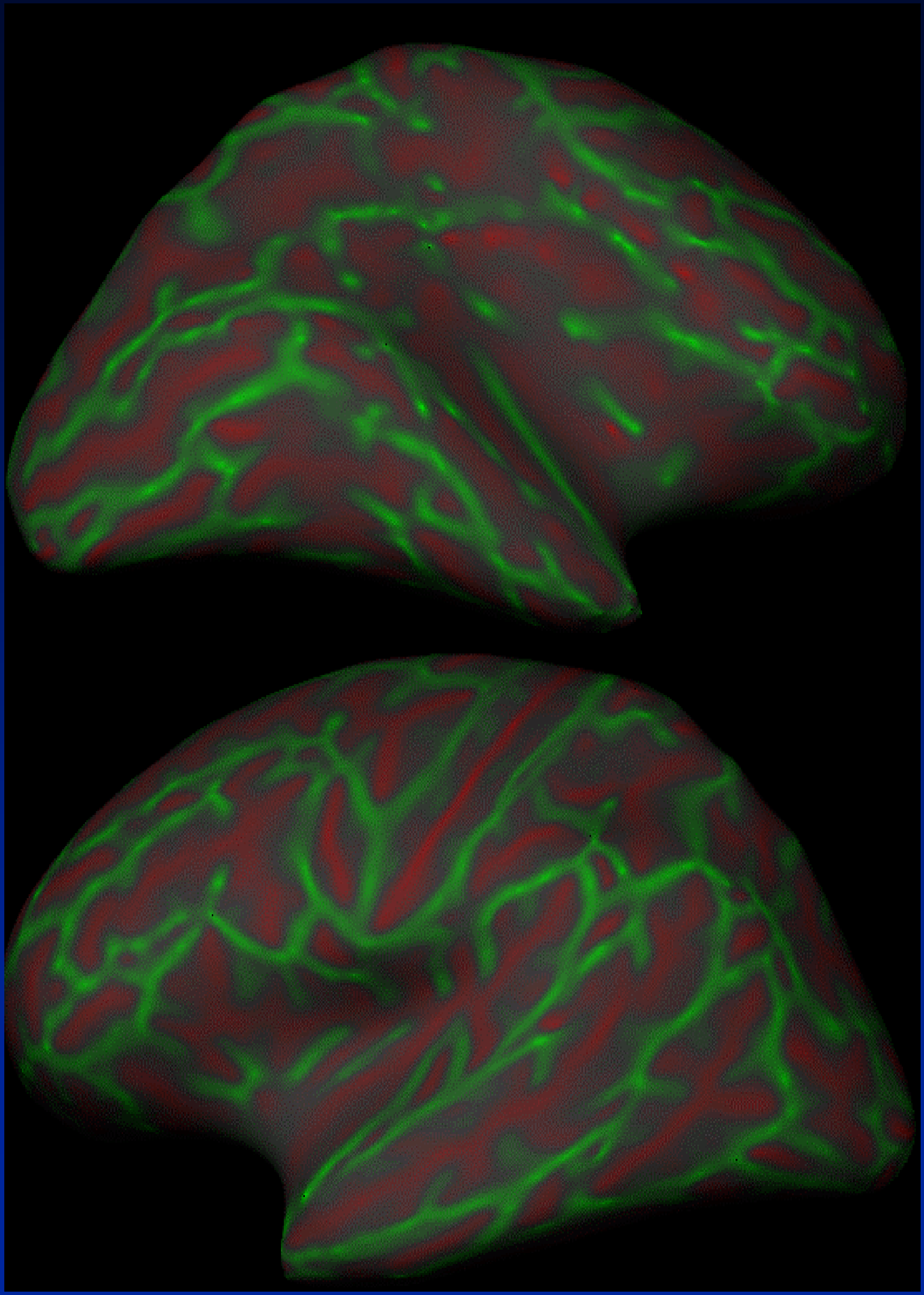
Rt

Lt



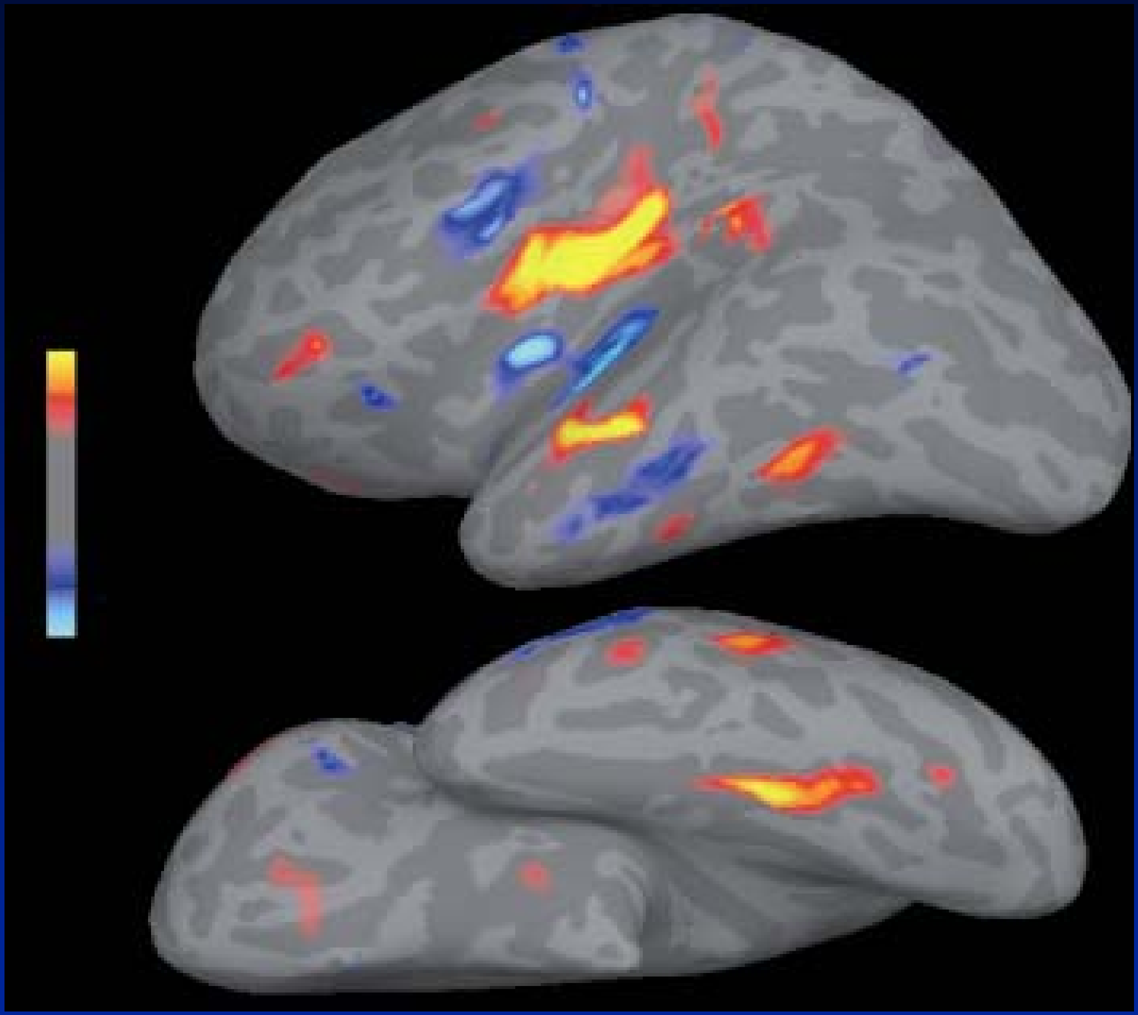
Right Hemisphere

Left Hemisphere



Fischl, Dale

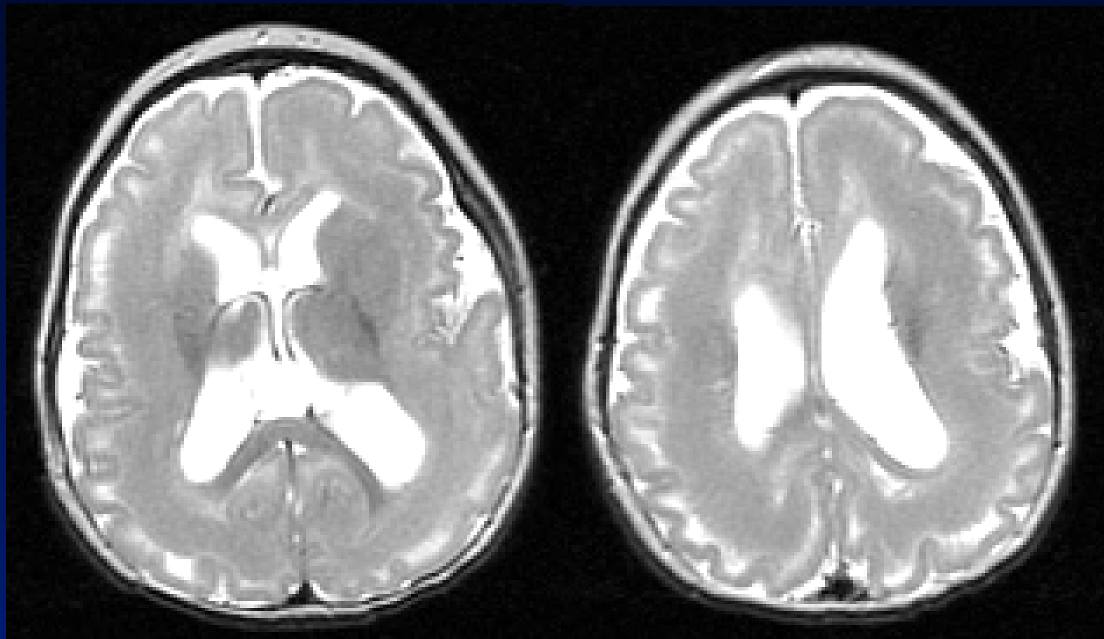
Statistical Comparison Of Right Hemisphere Compared to Normals



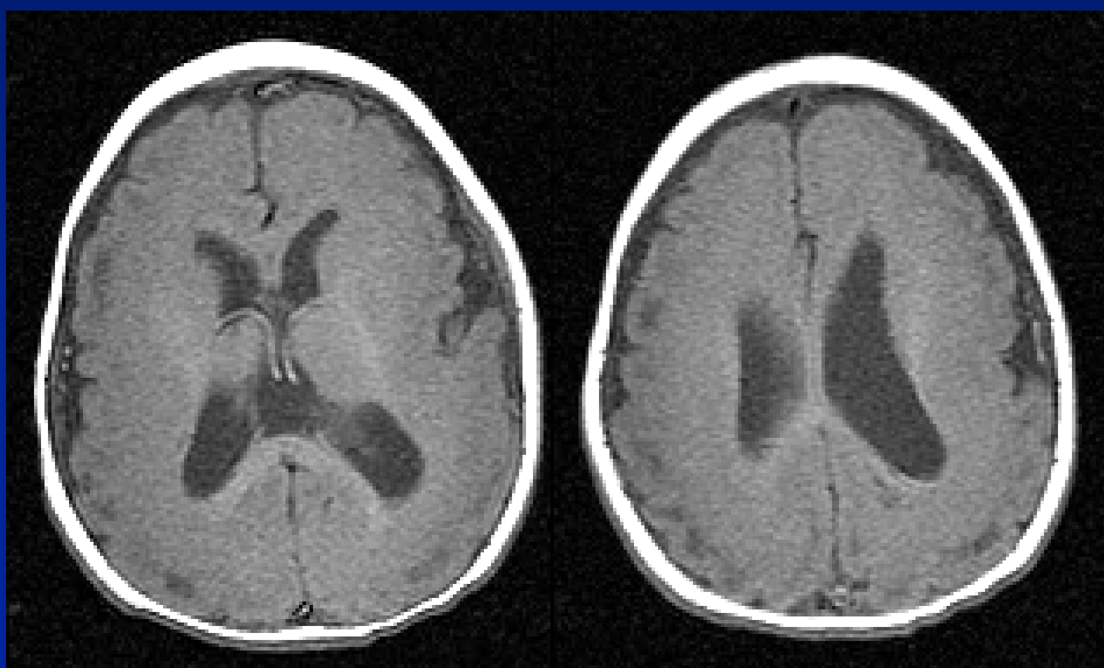
Fischl, Dale

Patient #1

- Patient CG-R is a 6 month-old developmentally normal Latina female presenting with 2 weeks of "spells", consisting of clusters of brief flexion at the waist accompanied by extension of the arms and eye-blinking, occurring 8-10 times daily. Her mother was diagnosed with generalized seizures in her teens, which have been well-controlled with single anti-epileptic agents. The patient's EEG showed hypsarrhythmia, and her clinical events were only marginally controlled with phenobarbital and valproate.

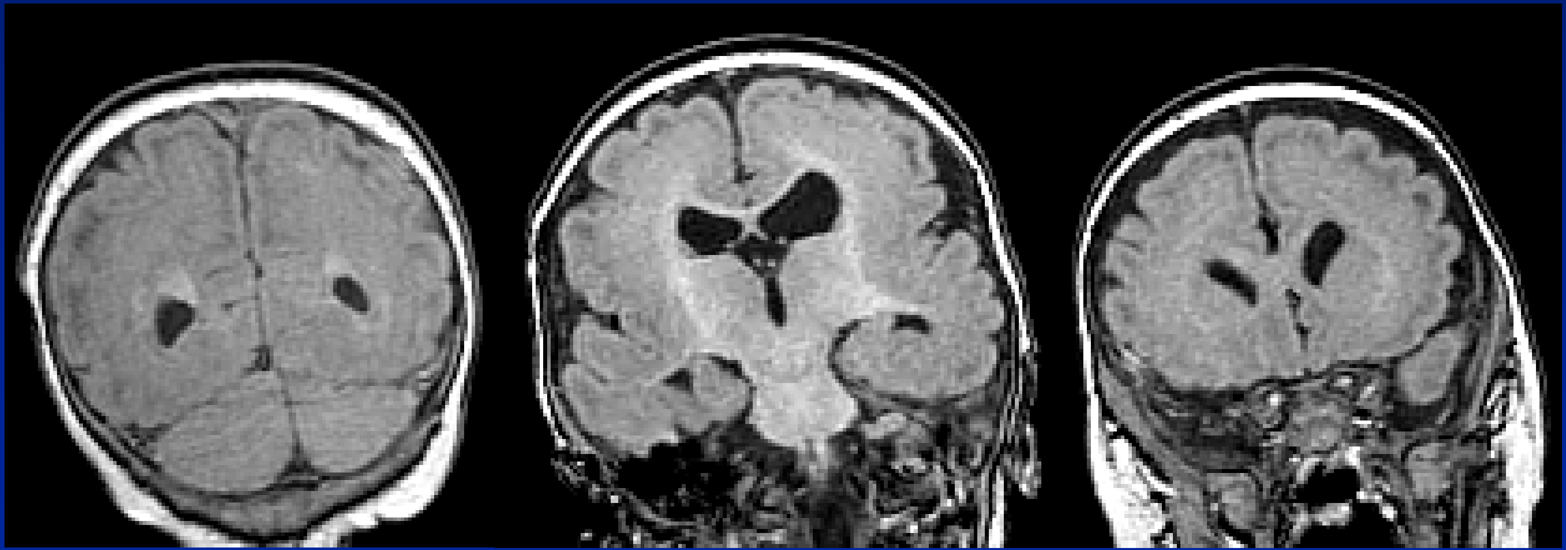


Axial T2 FSE

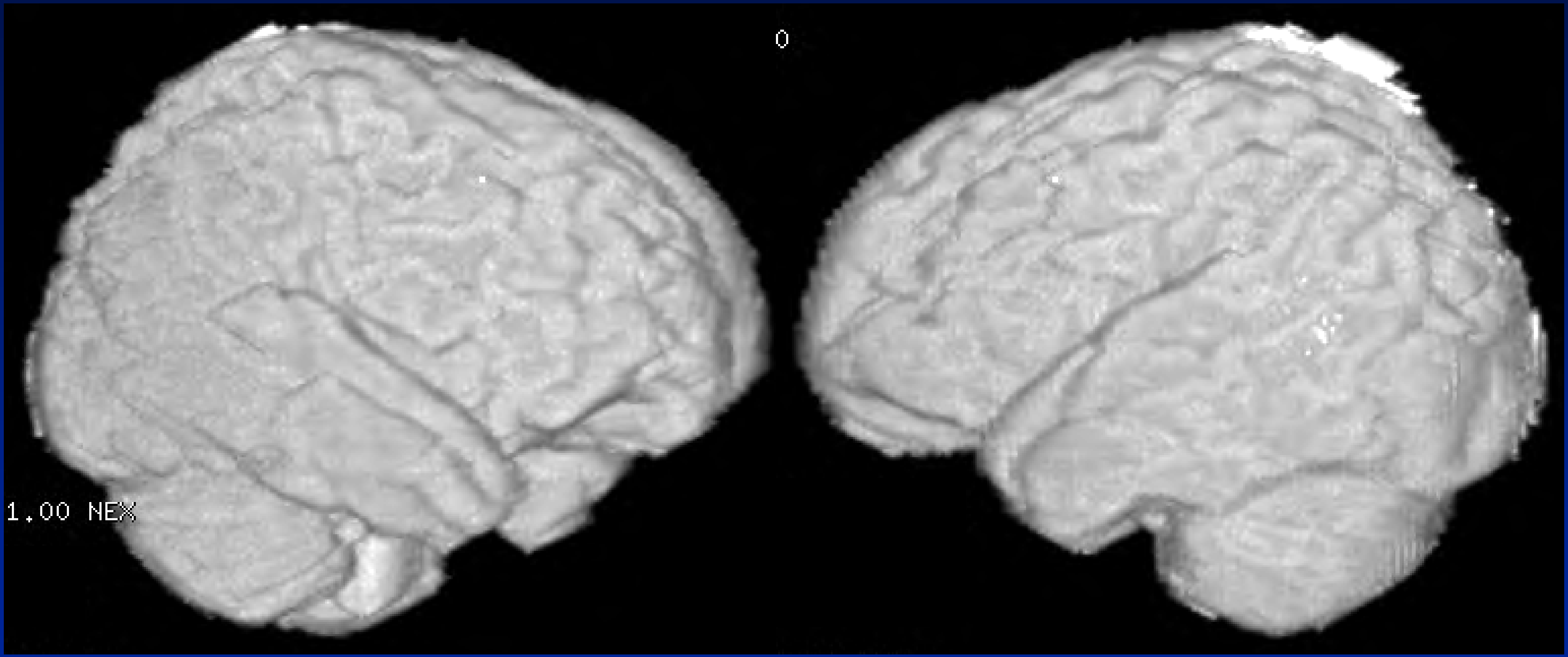


Axial T1

Coronal T2 FSE



Coronal 3DSPGR

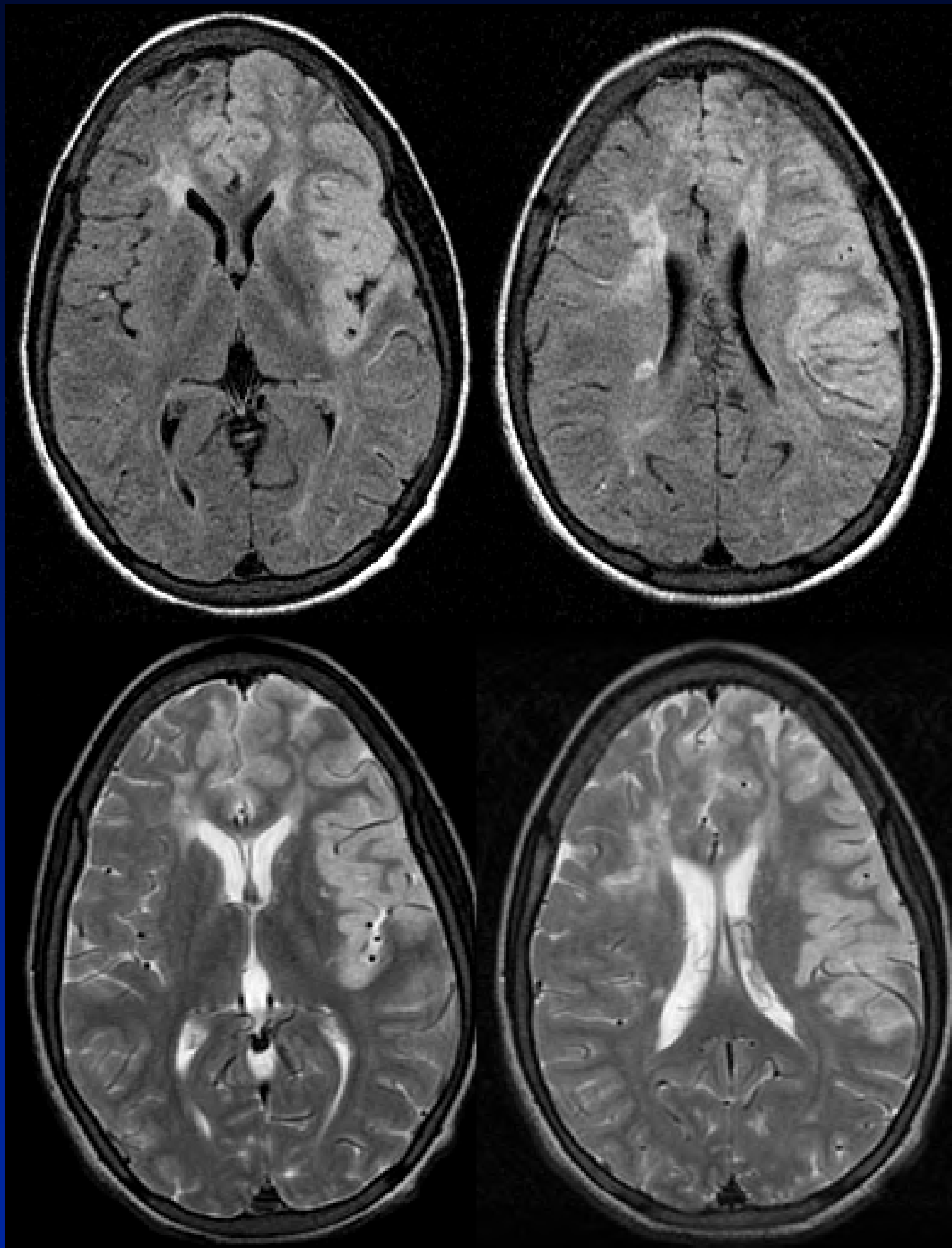


3D Surface Rending

Patient #2

- Patient CL is a 12 year old African-American male with history significant for sickle-cell anemia who had not been managed on transfusion therapy. In December of 2000, he presented with dysarthria and weakness of the right hand and arm which resolved over 24 hours. Exchange transfusions and regular pRBC transfusions were begun. In January of 2001, he presented with a dense right-sided hemiplegia and expressive aphasia. He was exchange transfused, and maintained at higher blood pressures for 48 hours, after which his symptoms resolved slowly. In rehabilitation he recovered near-normal right-sided motor function and improved speech. In April of 2001 he returned with worsening dysarthria, was exchange transfused, and is now improving slowly.

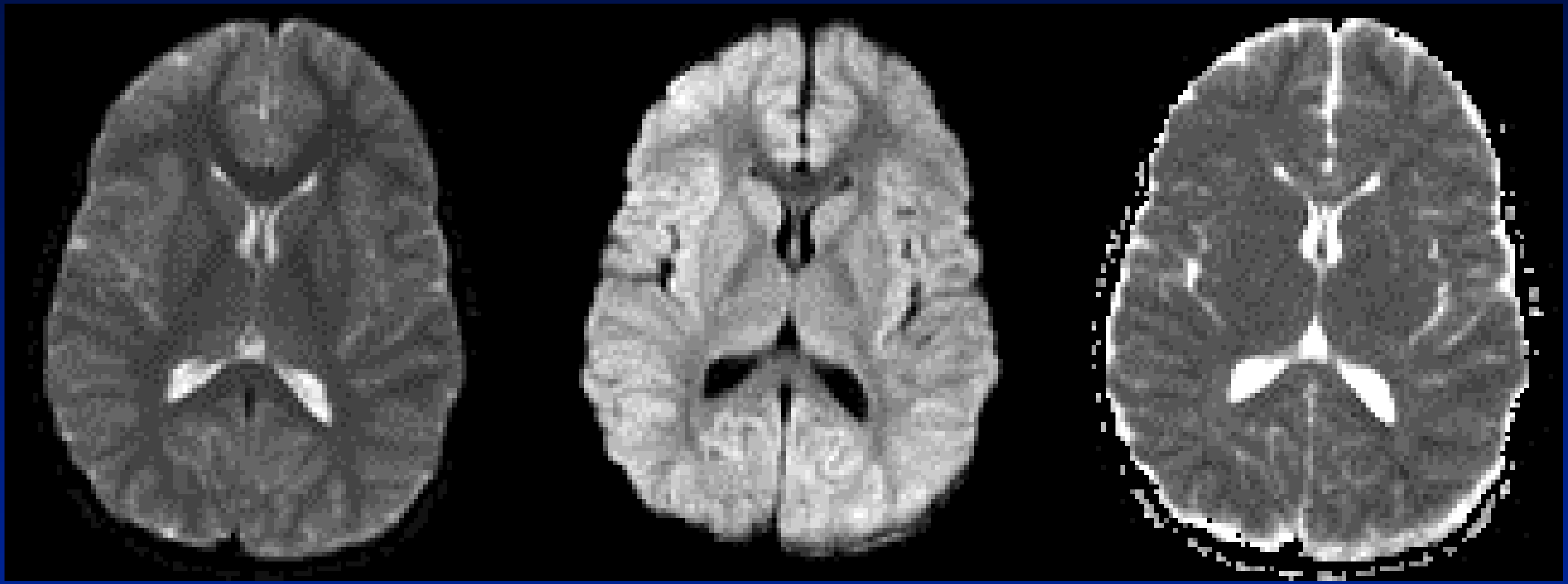
Post Contrast
Time Of Flight MR Angiogram



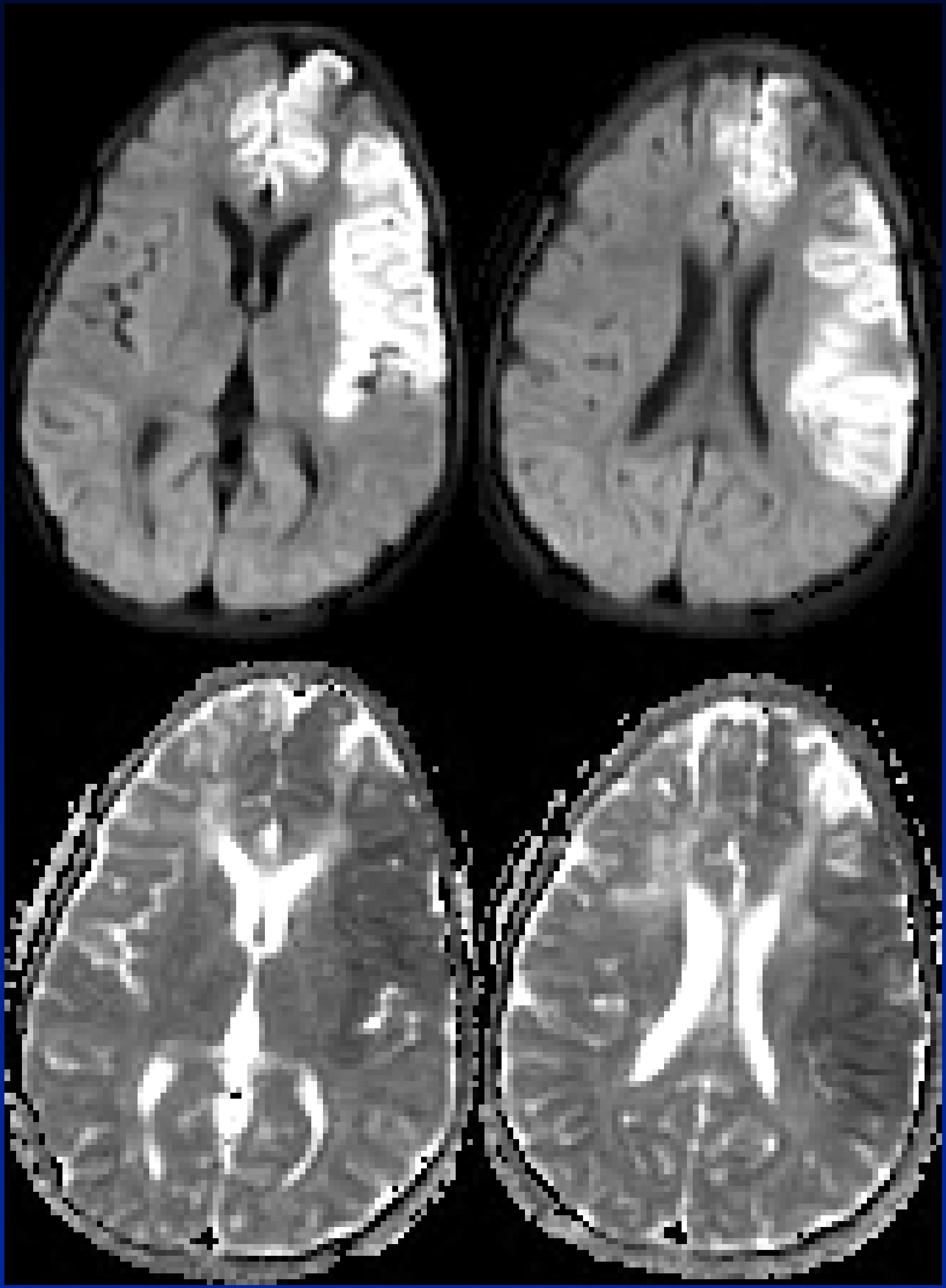
Axial FLAIR

Axial T2 FSE

EP T2 DWI ADC Map

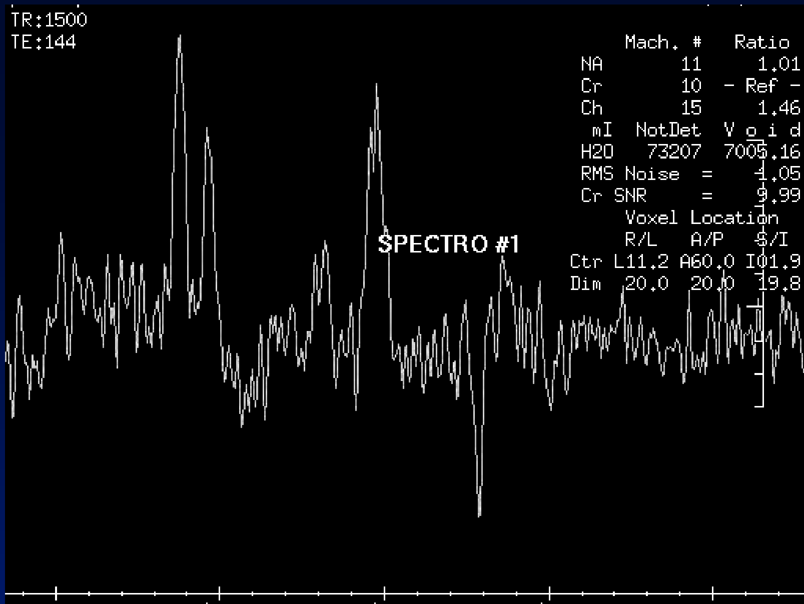


$S \sim S_0$ $S \sim S_0 e^{-b(ADC)}$ $S \sim ADC$

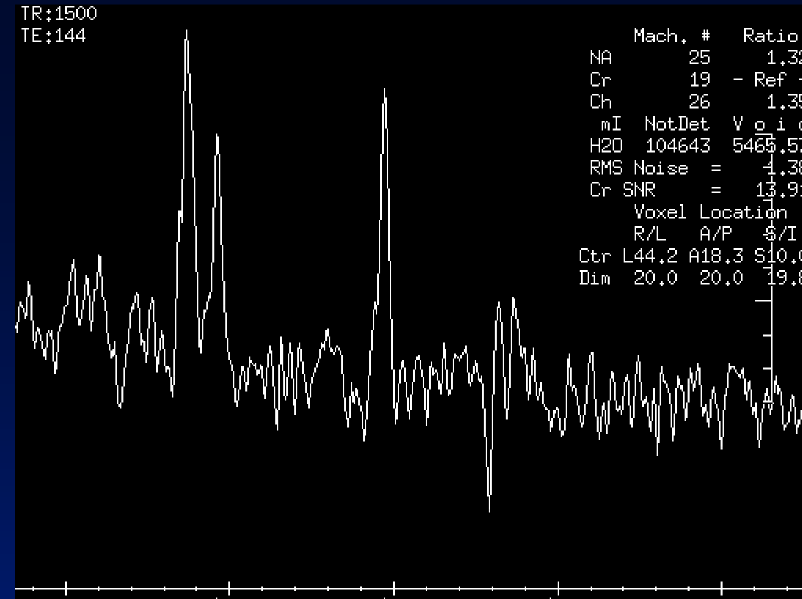


Axial DWI

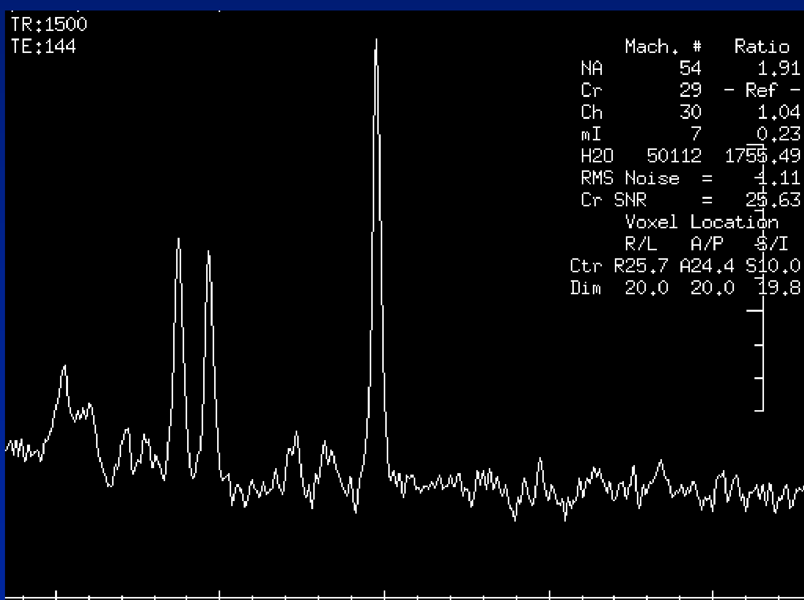
Axial ADC



Parasagittal Frontal Cortex



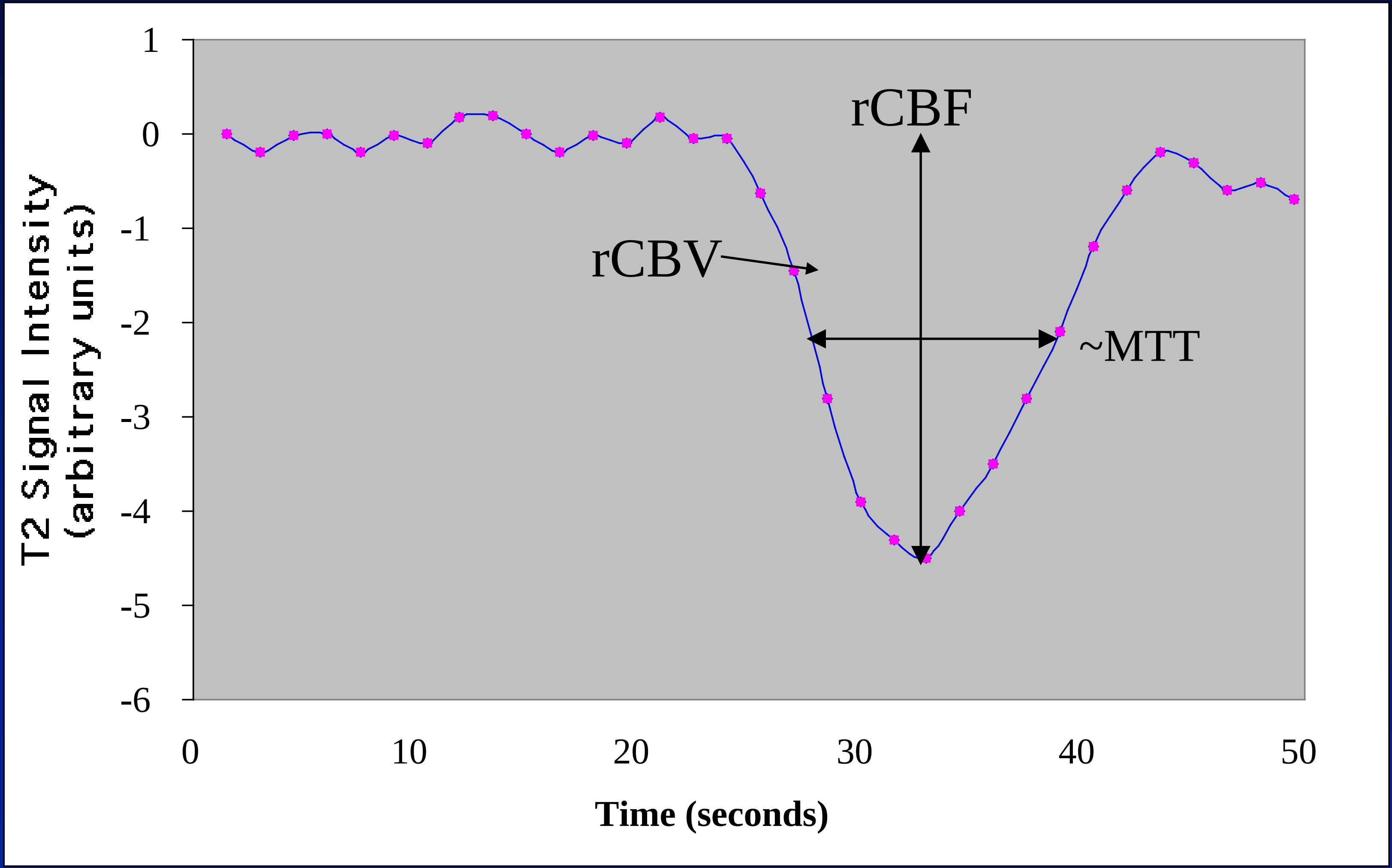
Left MCA Territory

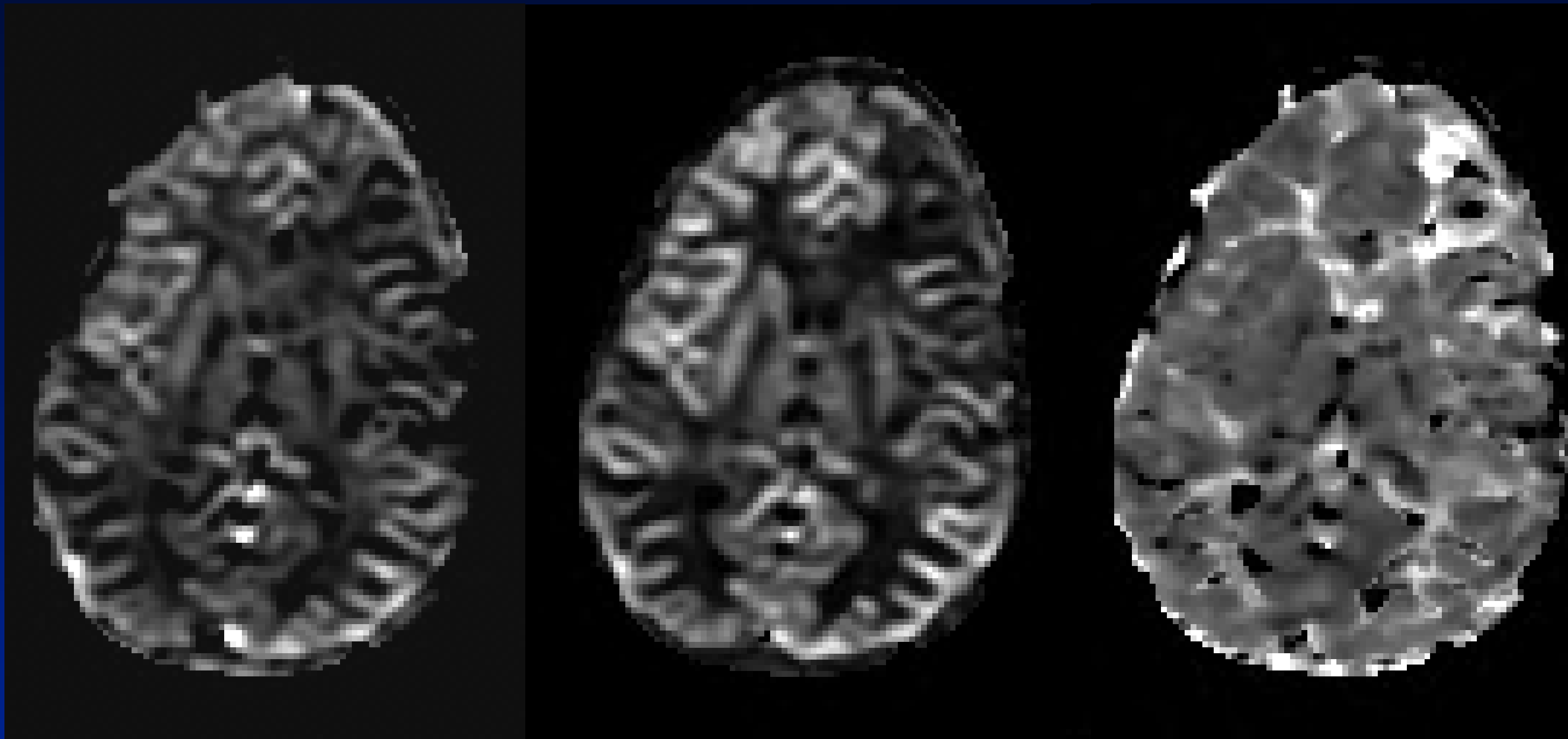


Right Centrum

^{1}H-MR Spectroscopy

Bolus Perfusion Imaging



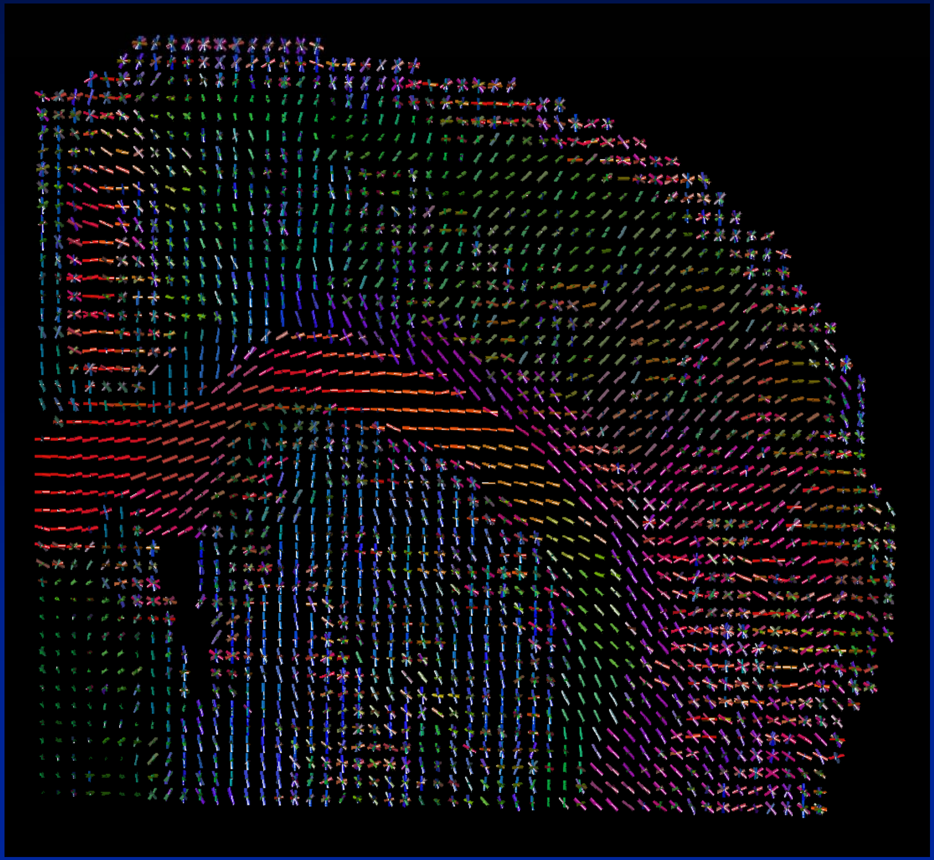


Relative Cerebral Blood Volume

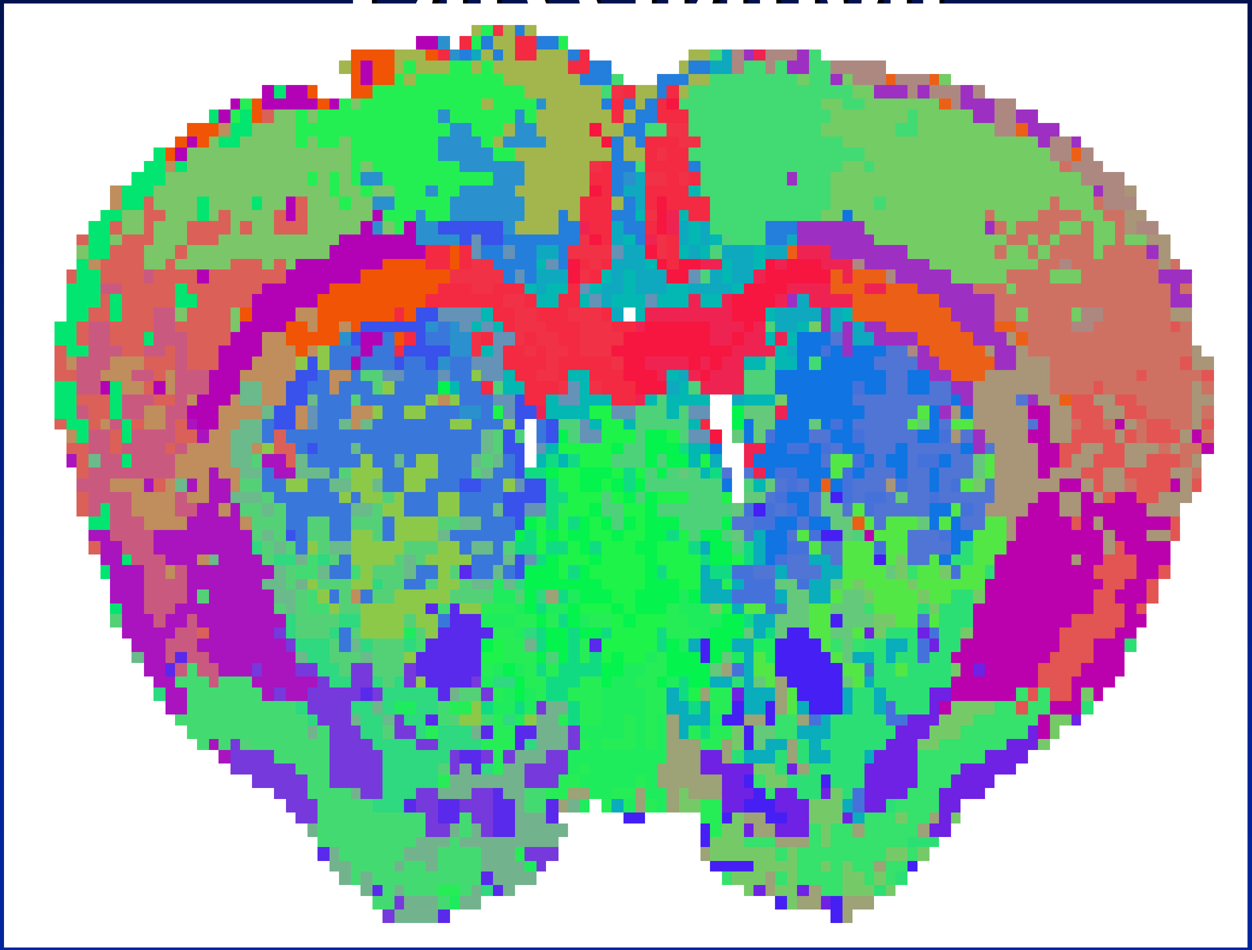
Relative Cerebral Blood Flow

Mean Transit Time

Mouse Brain: Coronal DSI



DSI (Diffusion Spectra Imaging) Automated Parcellation



Therapy for “Brain Attacks

- Alter cerebral perfusion
- Decrease ongoing “cell death”
  - Blunt ongoing brain damage
    - Calcium channel blockers (excitotoxicity)
  - Scavenge/Neutralize destructive molecules
    - Free radical scavengers (vitamin E)
- Decrease cell excitability
    - Antiepileptic drugs (barbituates)
    - Lower the brain temperature
- Promote growth and repair

Collaborators and Sponsors

- MGH-Neuroradiology
  - Ellen Grant, Larry Wald
- MGH-NMR Center
  - Van Wedeen, Anders Dale, Bruce Fischl, Nikos Makris, David Kennedy, Bruce Rosen
- Off-Site Collaborators
  - Pierre Gressens, Philippe Evrard, Barry Lester, Steve Sheinkopf, Victor Song
- 'Sponsors'
  - NIDA, Martinos Center

AN ELECTRONIC NOSE USED AS AN AID IN MEDICAL DIAGNOSES

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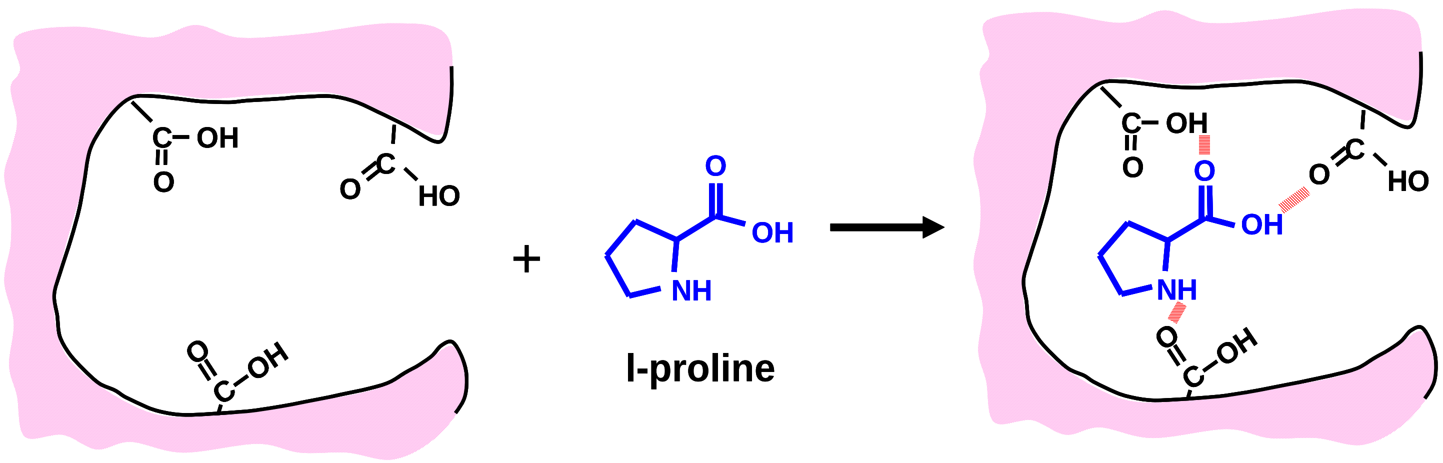
Jet Propulsion Laboratory
California Institute of Technology

CHEMICAL SENSING: "LOCK AND KEY" MODEL

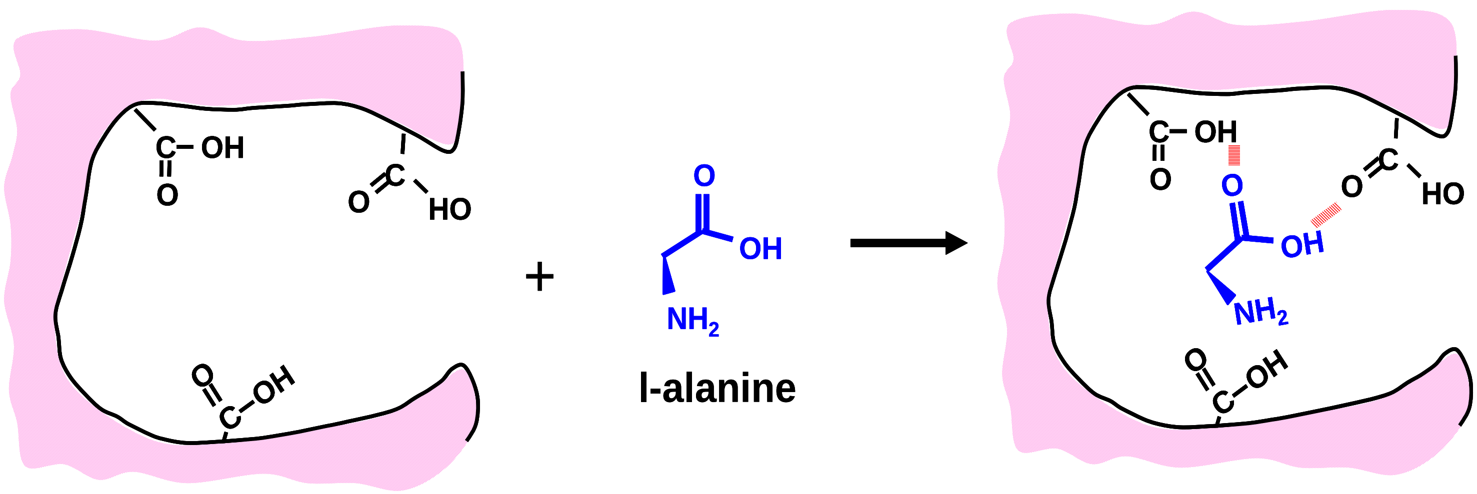
A molecule interacts with a unique receptor, triggering a response in the receptor. The fit may be shape and charge specific, or only shape specific. The response may be electrical (conductivity or potential) or optical (fluorescence or color); other transduction methods are possible



CHEMICAL SENSING: "LOCK AND KEY" MODEL

Jet Propulsion Laboratory
California Institute of Technology

Very few receptors are truly selective; there are generally cross-sensitivities which lend uncertainty to the sensing process. Cross sensitivity could be interpreted as low concentration of the targeted analyte.



CHEMICAL SENSING: SENSOR ARRAYS

ARRAY-BASED SENSING TAKES ADVANTAGE OF CROSS SENSITIVITIES IN CHEMICAL SENSORS

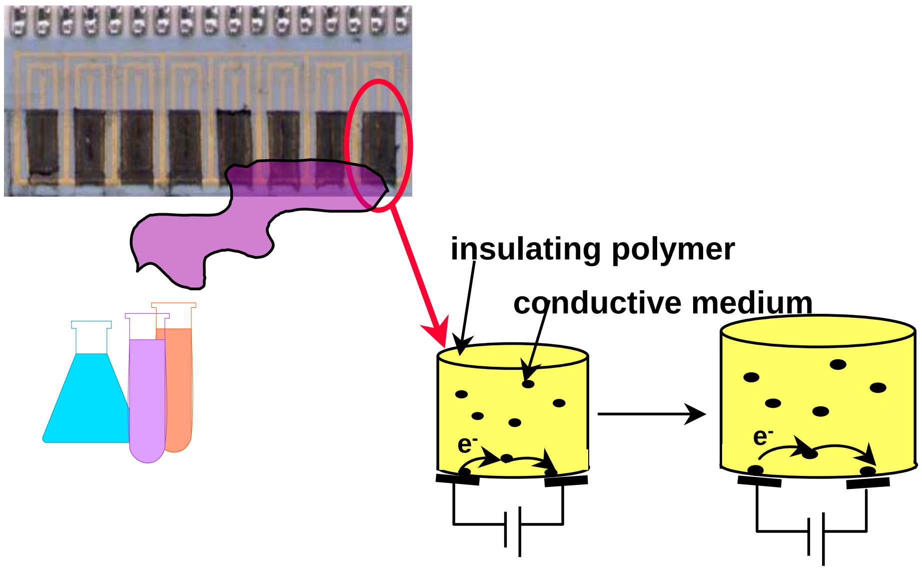
- **Elements in array are semi-selective toward target molecules**
- **Array responds in "fingerprint" pattern to stimulus**
- **Response of entire array is used to identify stimulant**

WHAT IS AN ELECTRONIC NOSE?

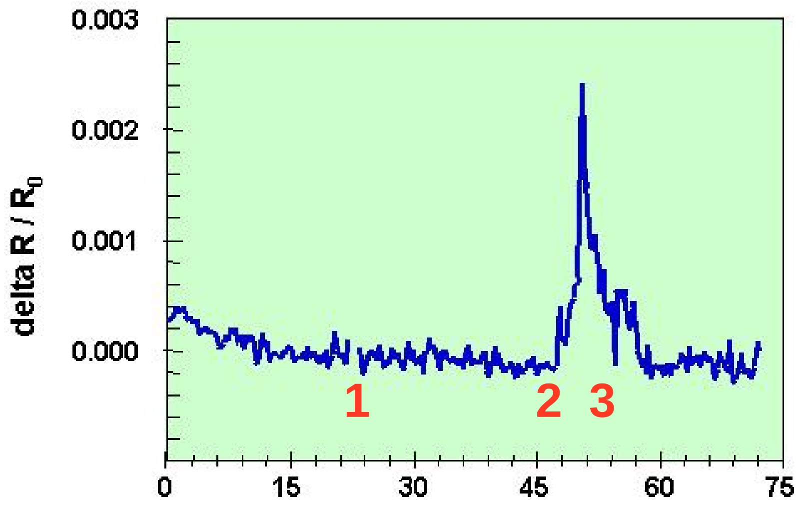
An array of non-specific chemical sensors, controlled and analyzed electron-ically, which have overlapping responses to compounds. Compounds are identified and quantified by recognition of patterns of response.

1. ENose measures background resistance in each sensor and establishes R_0 (baseline).

2. Contaminant comes in contact with and sorbs into sensors.

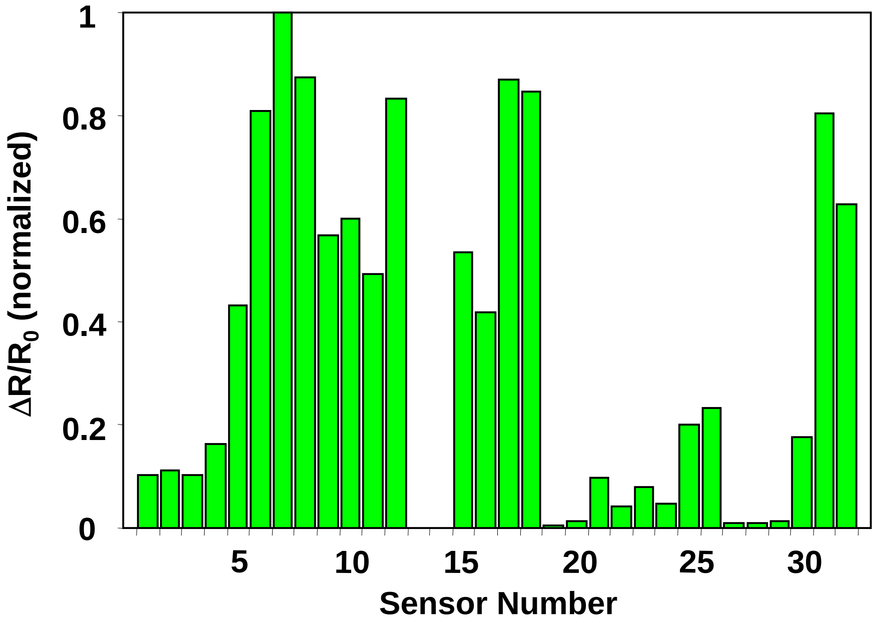


3. The sensors, polymer films loaded with a conductive medium such as carbon black, change resistance by swelling or shrinking as air composition changes.



WHAT IS AN ELECTRONIC NOSE?

4. Resistance is recorded, the change in resistance is computed, and the distributed response pattern ("fingerprint") of the sensor array is used to identify gases and mixtures of gases. The magnitude of response is used to quantify the identified compound.



5. Responses of the sensor array are analyzed and quantified using software developed for the task.

n-propanol, 30 ppm

Electronic Nose

FINGERPRINT RESPONSE OF ARRAY

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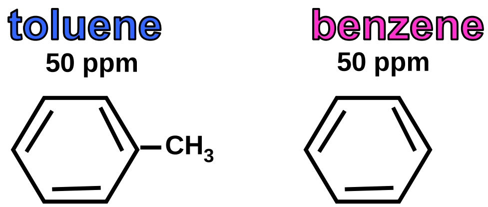
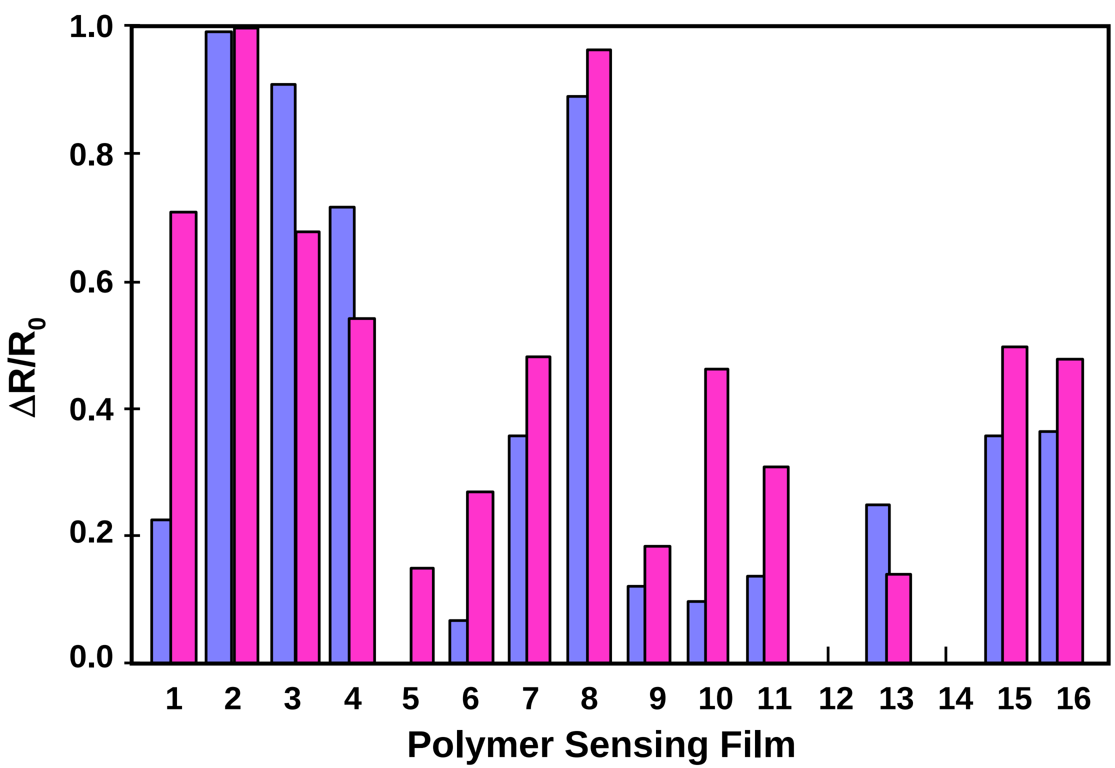


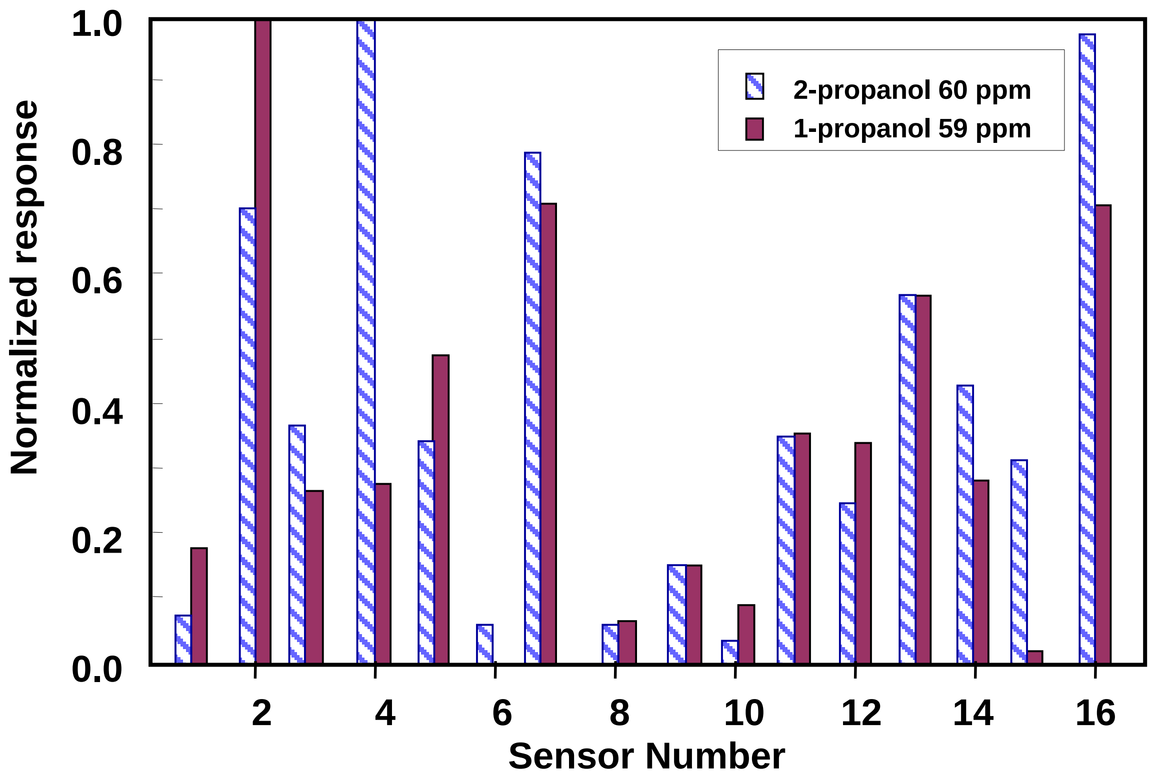


1 Poly(2, 4, 6-tribromostyrene)
2 Poly(4-vinylphenol)
3 Poly(ethylene oxide)
4 Polyamide resin
5 Cellulose triacetate
6 Poly(2-hydroxyethyl methacrylate)
7 Vinyl alcohol/vinyl butyral, 20/80
8 Poly(caprolactone)
9 Poly(vinylchloride-co-vinyl acetate)
10 Poly(vinyl chloride/acetate) 90/10
11 Poly(vinyl acetate)
12 Poly(N -vinylpyrrolidone)
13 Styrene/isoprene, 14/86 ABA
14 Poly(vinyl stearate)
15 Methyl vinyl ether/ maleic acid 50/50
16 Hydroxypropyl methyl cellulose, 10/30

Similar compounds can be distinguished by their fingerprints. Benzene and toluene are both aromatic, and have similar but distinguishable response patterns.

RESPONSE PATTERNS OF ISOMERS

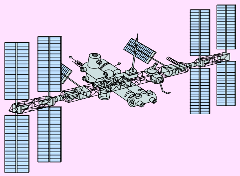
i-propanol n-propanol



1 Poly(2, 4, 6-tribromostyrene)
2 Poly(4-vinylphenol)
3 Poly(ethylene oxide)
4 Polyamide resin
5 Cellulose triacetate
6 Poly(2-hydroxyethyl methacrylate)
7 Vinyl alcohol/vinyl butyral, 20/80
8 Poly(caprolactone)
9 Poly(vinylchloride-co-vinyl acetate)
10 Poly(vinyl chloride/acetate) 90/10
11 Poly(vinyl acetate)
12 Poly(N -vinylpyrrolidone)
13 Styrene/isoprene, 14/86 ABA
14 Poly(vinyl stearate)
15 Methyl vinyl ether/ maleic acid 50/50
16 Hydroxypropyl methyl cellulose, 10/30

Isomers of propanol have similar but distinguishable response patterns.
Enantiomers can be distinguished by using chiral sensing films.

POSSIBLE APPLICATIONS

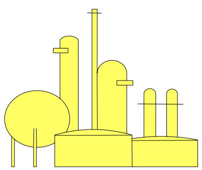


SPACE STATION ENVIRONMENTAL MONITORING

Event monitor for early warning of spills, leaks, fires; clean-up monitoring; automated environmental control.

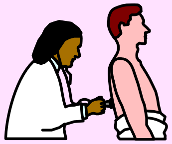
MILITARY APPLICATIONS

Air quality monitor for enclosed spaces.
Detection of explosives, chemical/biological warfare agents.



INDUSTRIAL MONITORING AND PROCESS CONTROL

Monitor food processing, identity and condition of raw materials, leaks and buildup of toxic compounds.



MEDICAL

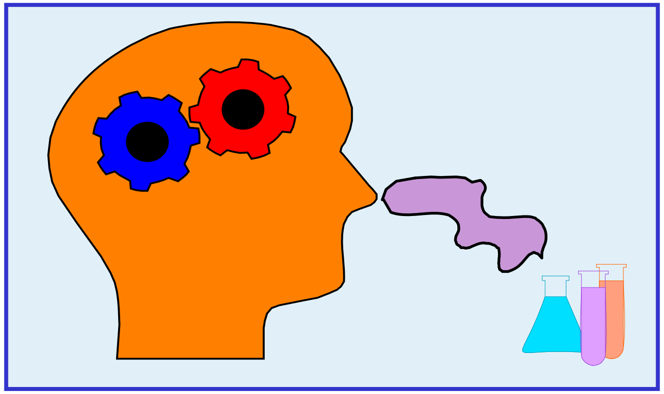
Diagnosis of diseases with characteristic odors, identify bacterial cultures, monitor patients' rooms, monitor labs.

OTHER ENVIRONMENTAL MONITORING

Air quality in buildings, aircraft. Presence of toxic materials in designated spaces.

Electronic Nose

REAL TIME AIR QUALITY MONITORING



HUMAN NOSE

- array of thousands of sensors
- broad band capability
- trainable to new odors
- data acquisition in the brain
- analysis by true Neural Network processing; pattern recognition

LIMITS ON HUMAN NOSE

- fatigue
- constant odor becomes background
- insensitivity to some compounds
- toxicity of some contaminants.

JPL ELECTRONIC NOSE

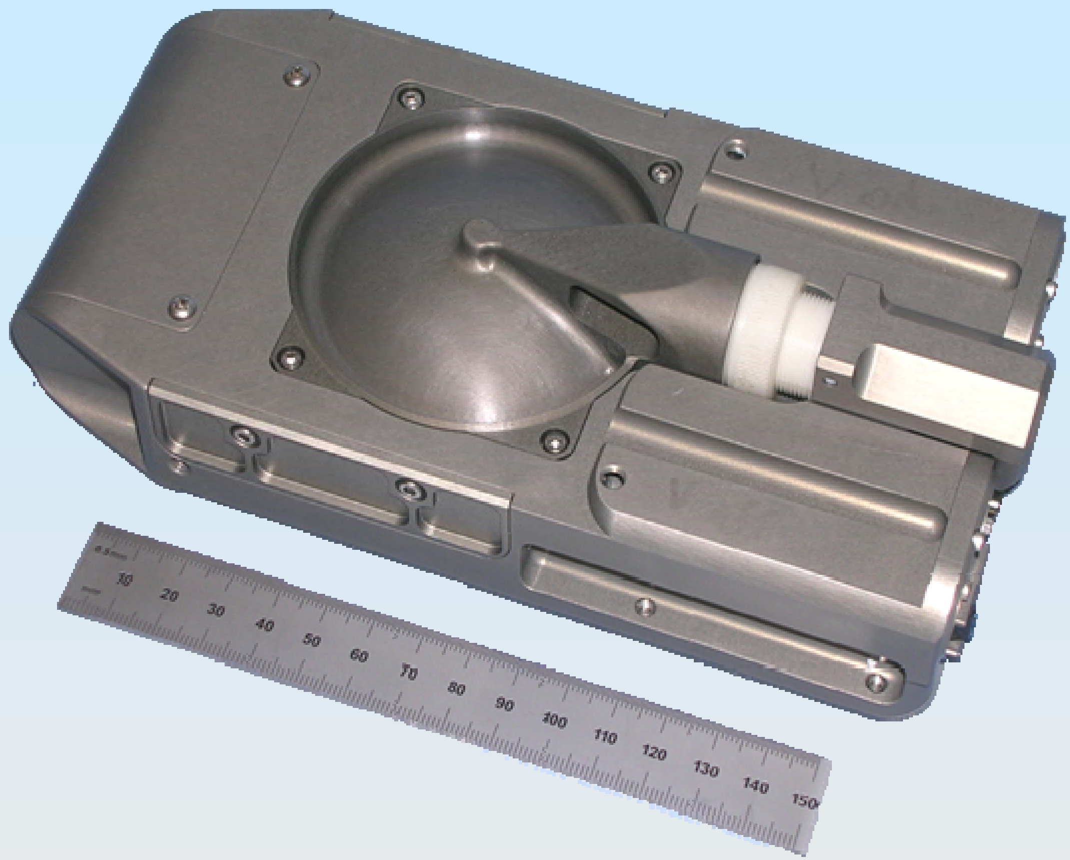
- array of a few tens of sensors
- thin film polymer based sensors
- broad band capability
- polymers selected to respond to particular compounds
- trainable to new analytes
- data acquisition by computer
- data analysis by computational methods and pattern recognition

LIMITS ON ENOSE

- insensitivity to some compounds; overcome by sensor film selection

ELECTRONIC NOSE SENSOR UNIT

Volume: 760 cm^3
Mass: 0.8 kg
Power: 10 W



The ENose Sensor Unit is a platform which can accept any of several sensing sets, selected for the analyte set to be detected. It requires a computer for operation, and can be run on a lap-top computer if real-time data analysis is required. Data can be collected on a PDA if analysis is to be done later on a more powerful computer.

ELECTRONIC NOSE TARGET COMPOUNDS

Chemical Species	Detected at JPL (ppm	mg/m³)	Chemical Species	Detected at JPL (ppm	mg/m³)
acetaldehyde	6	10	hydrazine	0.3	0.4
acetone	270	675	indole	0.03	0.15
acetonitrile	4	7	mercury	0.01	0.08
ammonia	20	13	methane	3000	2150
benzene	10	35	methanol	5	7
2-butanone	150	450	2-propanol	50	6
chlorobenzene	10	46	sulfur dioxide	1	3
dichloromethane	10	35	tetrahydrofuran	40	118
ethanol	50	25	1,1,1-trichloroethane	11	60
formaldehyde	25	30	toluene	15	56
Freon 113	20	160	xylenes	100	430
Freon 218	20	150	mixed compounds associated with overheating electronics		

SPACE STATION ENVIRONMENTAL MONITORING

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LONG-DURATION SPACE FLIGHT

- High level of crew productivity; little habitat maintenance
- Decouple environmental control from ground control
  - Distributed network of sensors and actuators
  - Sound an alarm and/or actuate remedial action
  - Early identification of areas requiring remediation

ELECTRONIC NOSE

- Incident monitor for leaks or spills resulting in contamination exceeding Spacecraft Max Allowable Concentration (SMAC)
- Monitor clean-up process
- Detect pre-combustion events

NASA'S INTEREST IN MEDICAL APPLICATIONS

LONG-DURATION SPACE FLIGHT

- Crews of 2-5 persons for 3 months to 2 years
  - ISS missions 3 months
  - Moon missions 6-12 months
  - Mars missions ~ 2 years
- ISS and Moon missions have 1-4 day return time in medical emergency; Mars missions have 7-12 month return time.
- Dependence on local diagnosis and care. One crew member may be MD.
- NASA requires development of small, low power diagnostic and treatment aids for use in local care and in telemedicine

ELECTRONIC NOSE

In the last few years, there have been several *in vitro* and *in vivo* studies of diagnosis using an electronic nose

CLINICAL STUDIES USING AN ELECTRONIC NOSE

BREATH ANALYSIS

Exhaled breath is collected in a sampling bag or patient breathes directly into device. Exhaled breath may contain several tens of volatile organic compounds as well as water vapor

SWAB HEADSPACE ANALYSIS

Liquid (sweat, sputum, infection site) collected on a swab; swab enclosed and headspace sampled to detect bacterial metabolic products.

ODOR ANALYSIS

Device used to “sniff” patient to detect chemical species which signal diseases

CULTURE HEADSPACE ANALYSIS

Headspace above a culture plate is sampled to detect metabolic or other products

ARRAY RESPONSE TO A COMPLEX MIXTURE

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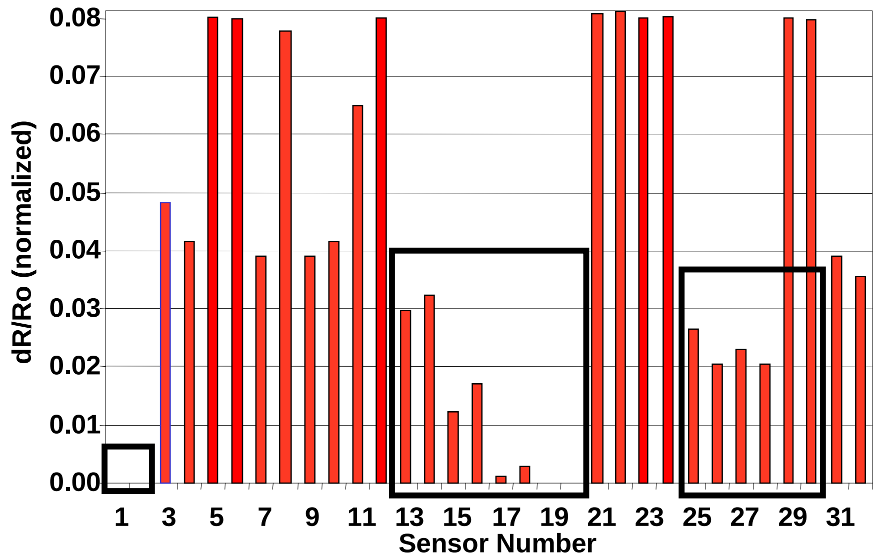
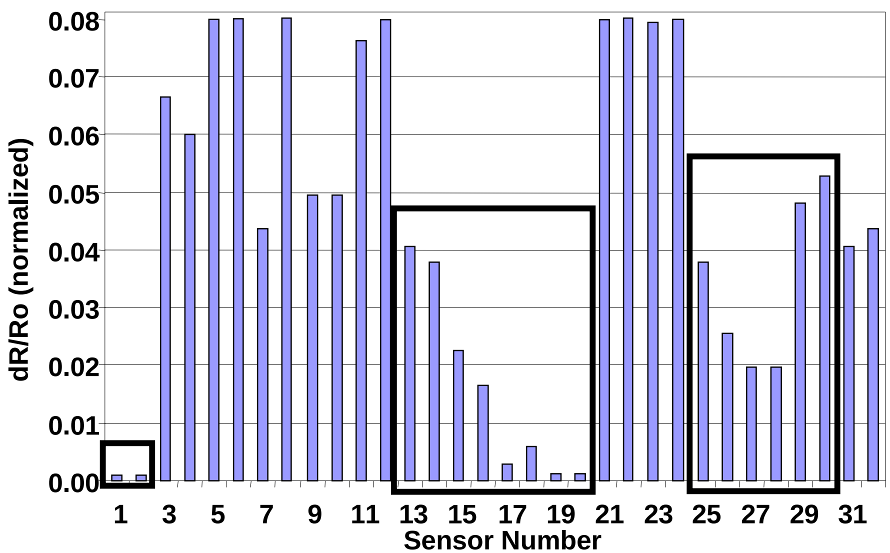
California Institute of Technology

Complex mixtures can be treated as a single analyte by an electronic nose. In the absence of other chemical species, or in the presence of an unchanging background, the complex mixture will yield a single array response pattern.

This figure shows how Coca-Cola and Pepsi-Cola have similar but distinguishable array response patterns





Studies Using Breath Analysis for Diagnosis

Pneumonia (VAP) 80% accuracy

- **detection of VOC markers**
- **correlated with CT scans, other clinical data**

Hanson, C.W. and Thaler, E.R. Electronic Nose Prediction of a Clinical Pneumonia Score: Biosensors and Microbes. Anesthesiology 102, 63-68 (2005).

Hockstein, N.G., Thaler, E.R., Lin, Y.Q., Lee, D.D., and Hanson, C.W. Correlation of Pneumonia Score With Electronic Nose Signature: a Prospective Study. Annals of Otology Rhinology and Laryngology 114, 504-508 (2005).

Diabetes mellitus

- **detection of acetone**
- **correlated with clinical data**

Yu, J.B., Byun, H.G., So, M.S., and Huh, J.S. Analysis of Diabetic Patient's Breath With Conducting Polymer Sensor Array. Sensors and Actuators B-Chemical 108, 305-308 (2005).

MEDICAL APPLICATIONS OF ELECTRONIC NOSES

Studies Involving Fluid Analysis (sweat or swabs)

Schizophrenia >95% accuracy

- **variation in body odor**
- **discrimination from other mental illness and controls**

Di Natale, C. *et al.* Identification of Schizophrenic Patients by Examination of Body Odor Using Gas Chromatography-Mass Spectrometry and a Cross-Selective Gas Sensor Array. Medical Science Monitor 11, CR366-CR375 (2005).

Renal Dysfunction 95% accuracy

- **variation in body odor (acid/base balance & electrolytes)**
- **discrimination among end stage/chronic/no renal failure**

Voss, A. et al. Smelling Renal Dysfunction Via Electronic Nose. Annals of Biomedical Engineering 33, 656-660 (2005).

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Studies Involving Fluid Analysis (sweat or swabs)

Tuberculosis 90% accuracy

- **bacterial metabolic products *in vitro* or swab headspace discrimination among various bacteria**
- **correlated with cultured swabs**

Pavlou, A.K. *et al.* Detection of Mycobacterium Tuberculosis (Tb) in Vitro and in Situ Using an Electronic Nose in Combination With a Neural Network System. Biosensors & Bioelectronics 20, 538-544 (2004).

ENT Infection (S. aureus) 88% accuracy

- **swab headspace discrimination among three bacteria subclasses**
- **correlated with cultured swabs**

Dutta, R., Gardner, J.W., and Hines, E.L. Classification of Ear, Nose, and Throat Bacteria Using a Neural-Network-Based Electronic Nose. Mrs Bulletin 29, 709-713 (2004).

Shykhon, M.E., Morgan, D.W., Dutta, R., Hines, E.L., and Gardner, J.W. Clinical Evaluation of the Electronic Nose in the Diagnosis of Ear, Nose and Throat Infection: a Preliminary Study. Journal of Laryngology and Otology 118, 706-709 (2004).

Olfactory Detection of Cancers

Tumor-Sniffing Dogs

- **Studies of canine detection: lung, breast, bladder, skin**

Trained dogs detect presence of cancer through breath, fluid or direct odor analysis. High level of accuracy (85-95%)

Mcculloch, M. *et al.* Diagnostic Accuracy of Canine Scent Detection in Early- and Late-Stage Lung and Breast Cancers. Integrative Cancer Therapies 5, 30-39 (2006).

Pickel, D., Manucy, G.P., Walker, D.B., Hall, S.B., and Walker, J.C. Evidence for Canine Olfactory Detection of Melanoma. Applied Animal Behaviour Science 89, 107-116 (2004).

Willis, C.M. et al. Olfactory Detection of Human Bladder Cancer by Dogs: Proof of Principle Study. British Medical Journal 329, 712-714A (2004).

- **News Reports: brain, breast, lung, skin, bladder**

Olfactory Detection of Cancers

Electronic Nose

Studies for detection of lung cancer using two different e-noses; 70 - 90% accuracy

- **detection of VOC markers**
- **correlated with clinical data**

Di Natale, C. et al. Lung Cancer Identification by the Analysis of Breath by Means of an Array of Non-Selective Gas Sensors. Biosensors & Bioelectronics 18, 1209-1218 (2003).

Machado, R.F. et al. Detection of Lung Cancer by Sensor Array Analyses of Exhaled Breath. American Journal of Respiratory and Critical Care Medicine 171, 1286-1291 (2005).

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Why Would Tumors Have An Odor Signature?

Studies of volatile organic compounds produced by tumors show it is possible to classify by VOCs

Studies of differences in protein structure of cancerous and normal tissues

Studies of volatile organic markers in breath of cancer patients

MEDICAL APPLICATIONS OF ELECTRONIC NOSES

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California Institute of Technology

Advantages of Diagnosis with an Electronic Nose

- **Instruments are portable, in some cases hand-held, relatively inexpensive and do not require extensive training or laboratories for use**
- **Analysis of data can be accomplished in several minutes**
- **Sample collection is simple**
  - **vapor phase samples drawn directly into device**

    or
  - **fluids placed into receptacle and headspace sampled**

    or
  - **take swab, hold in vitro 30-120 minutes, moderate or no heat**

Limitations of Diagnosis with an Electronic Nose

- **Studies generally have samples of 10-100 patients and so do not yet show general applicability**
- **Breath analysis requires careful adjustment of responses of sensors to water vapor**
- **Several studies tried multiple approaches to data analysis before finding one which gave high correlation with control or other clinical data**
- **Marker compounds for diseases are not always well characterized; use for diagnosis of different diseases will require different sets of sensors and specific data analysis routines**
- **Other odors may interfere with sensor response**

CONCLUSIONS

Electronic Noses Show Promise for Medical Application

- **An electronic nose could be a powerful tool for early, preliminary diagnoses, to be followed by further collection of clinical data**
- **Diagnosis using an electronic nose would probably not be global; specific sensor sets will correspond to detection of specific diseases**
- **Potential applications to telemedicine and for delivery of medical care to remote sites**

ACKNOWLEDGMENTS

The JPL ENose team thanks Babak Kateb and Mike Chen of City of Hope Cancer Center for initiating studies of use of the ENose in tumor detection.

The JPL ENose development program is funded by NASA, Exploration Systems Mission Directorate, Life Support and Habitation Program, Advanced Environmental Monitoring and Control Project.

The research reported here was carried out at the Jet Propulsion Laboratory, California Institute of Technology under a contract with the National Aeronautics and Space Administration.

In-vitro Analysis of Cells and Tissues using the Electronic Nose

Babak Kateb

Mike Y. Chen

Jet Propulsion Laboratory
California Institute of Technology

NASA

City of Hope

Objective

- Long term objectives:
  - 1) To determine if Enose can be used to distinguish tumor tissue from normal tissue
  - 2) To investigate if the Enose can also be used to "classify" tumors

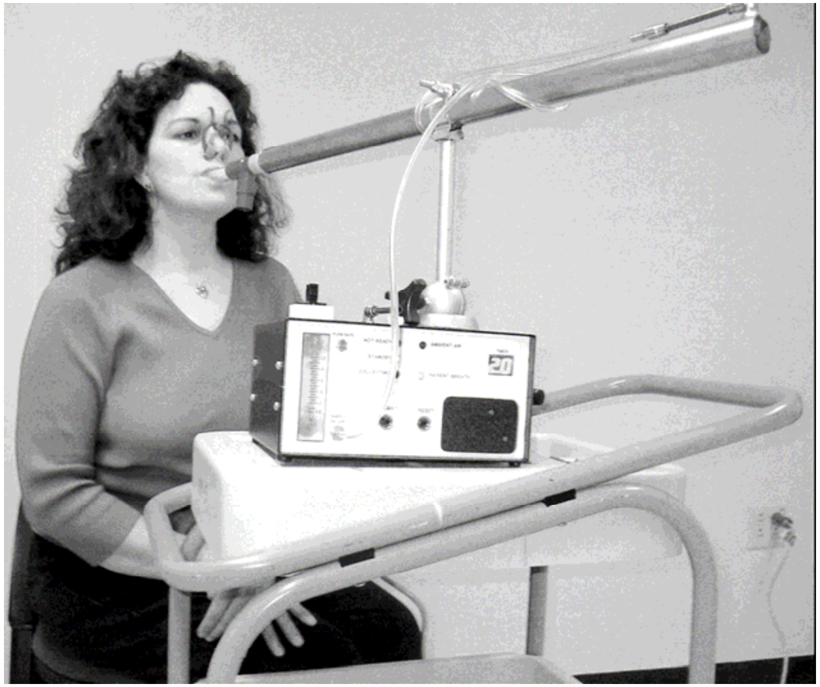
- Hypothesis: Tissues, normal or pathological, will have distinct Enose “fingerprints.”

Background

- Carolyn Willis et al. (2004): 6 dogs, 7 mo. training, 41% success rate vs. 14% by chance
- Pickel et al. (2004): 2 dogs able to discriminate between covered decoy and melanoma lesions

Enose: Lung cancer

- Philips et al. (2003): volatile organic compounds (Alkanes and monomethylated alkanes) measured using gas chromatography and mass spectroscopy as the basis of a predictive model



Enose: Lung cancer

Lung cancer identification by the analysis of breath by means of an array of non-selective gas sensors

Corrado Di Natale[a,b,*], Antonella Macagnano[b], Eugenio Martinelli[a], Roberto Paolesse[b,c], Giuseppe D'Arcangelo[c], Claudio Roscioni[d], Alessandro Finazzi-Agrò[e], Arnaldo D'Amico[a,b]

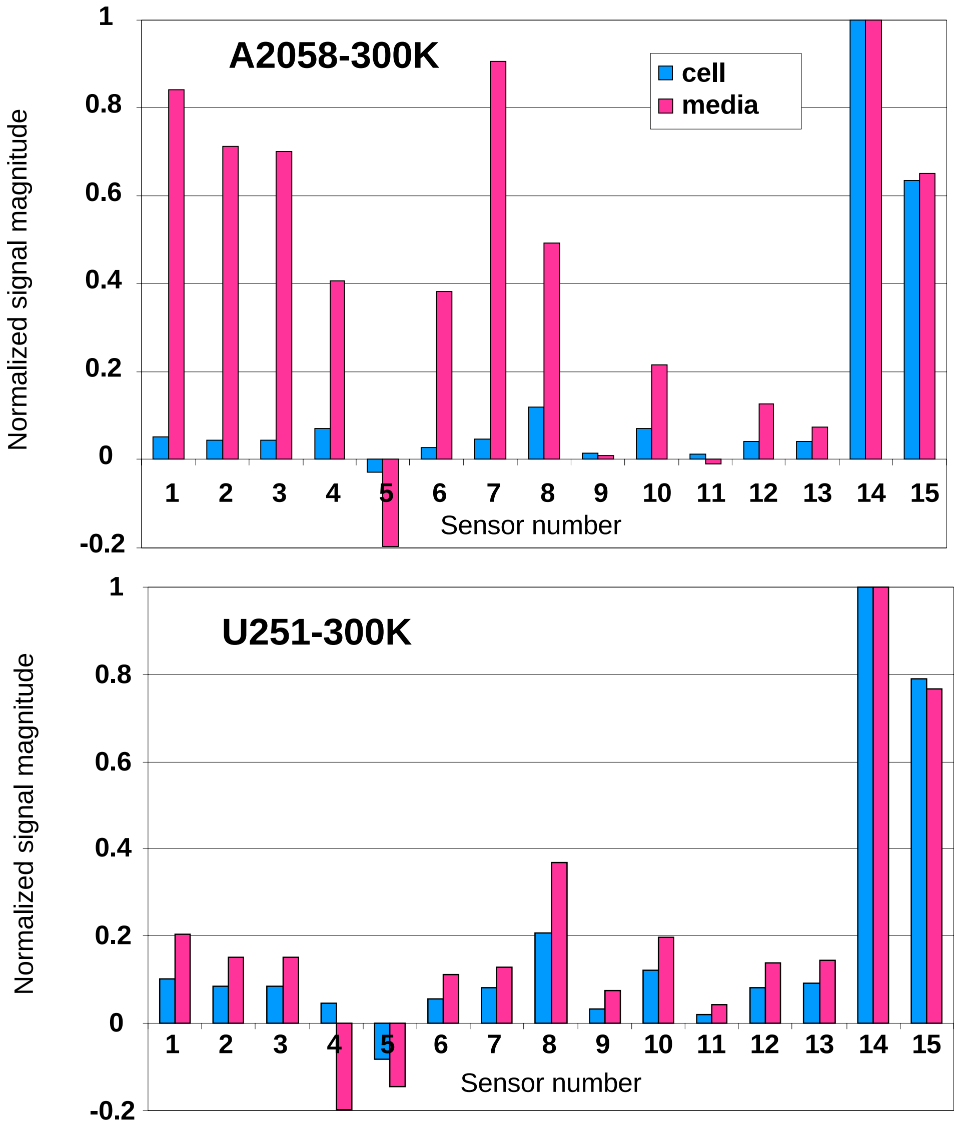
- Di Natale et al. (2002): were able to distinguish exhaled air of 35 lung cancer patients from 19 controls

- Aim: To investigate if the Enose can distinguish:
  - Different tumor types in cell culture
  - Different tissue types

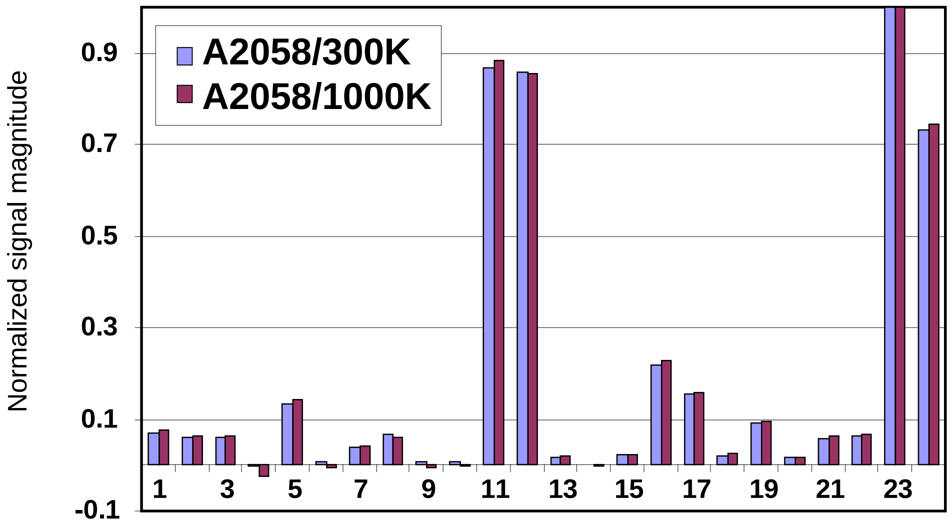
Methods

- Cell lines:
  - A2058 Melanoma
  - U251 Glioblastoma
- Tissues:
  - Puréed chicken liver
  - Puréed chicken muscle
- Device: JPL Enose

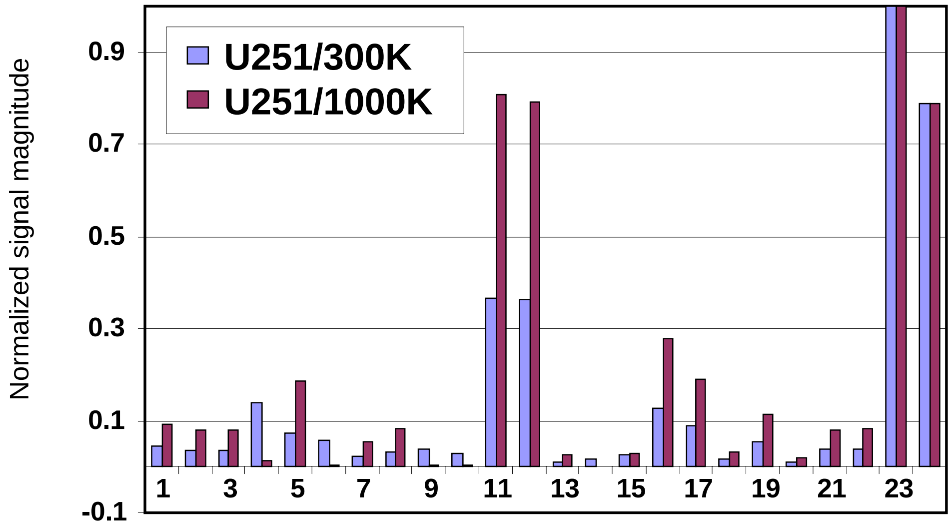
Effect of Culture Media



Effect of starting cell number

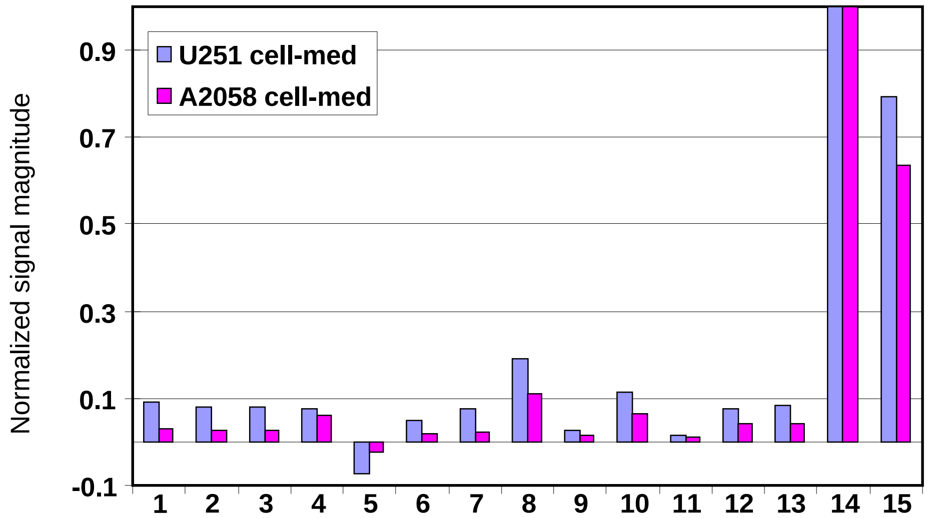


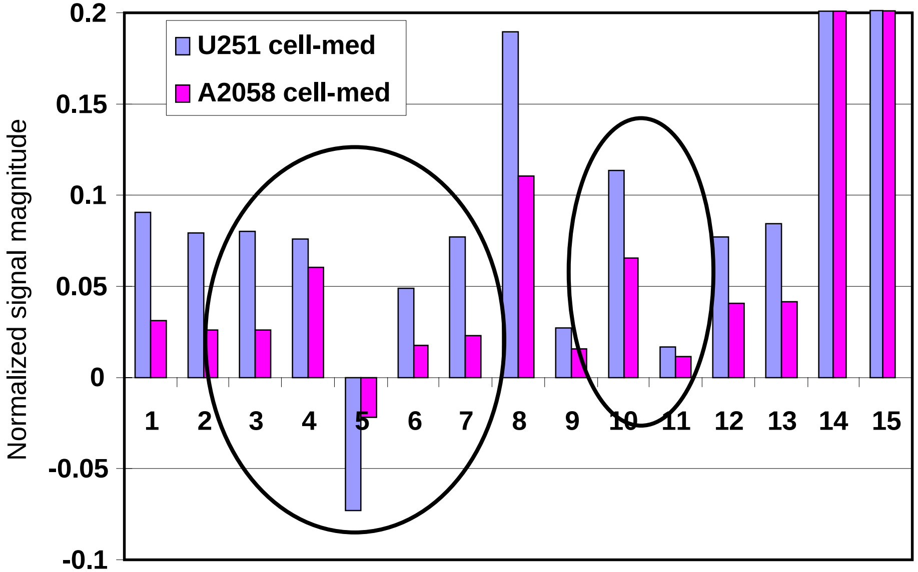
Array variation 8%



Array variation 49%

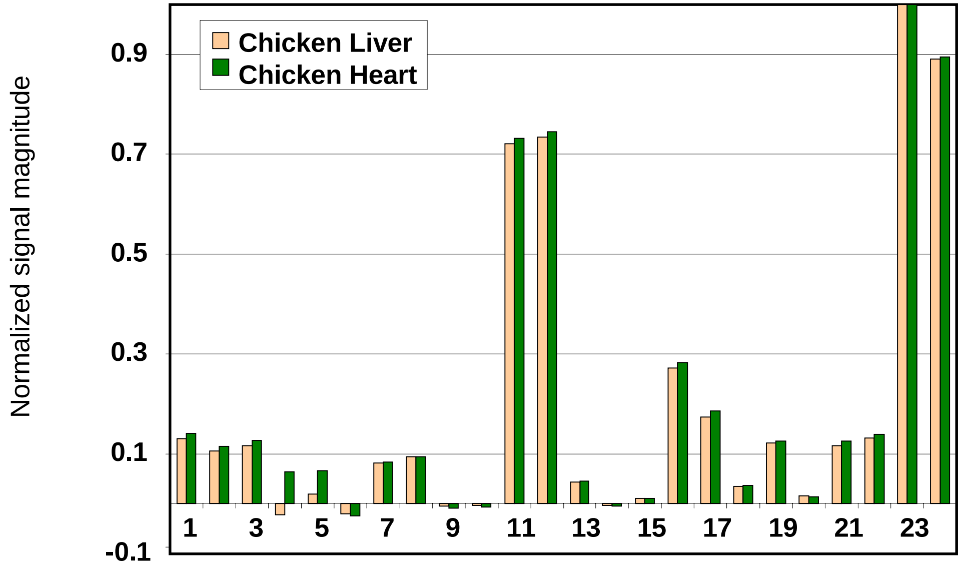
U251 versus A2058

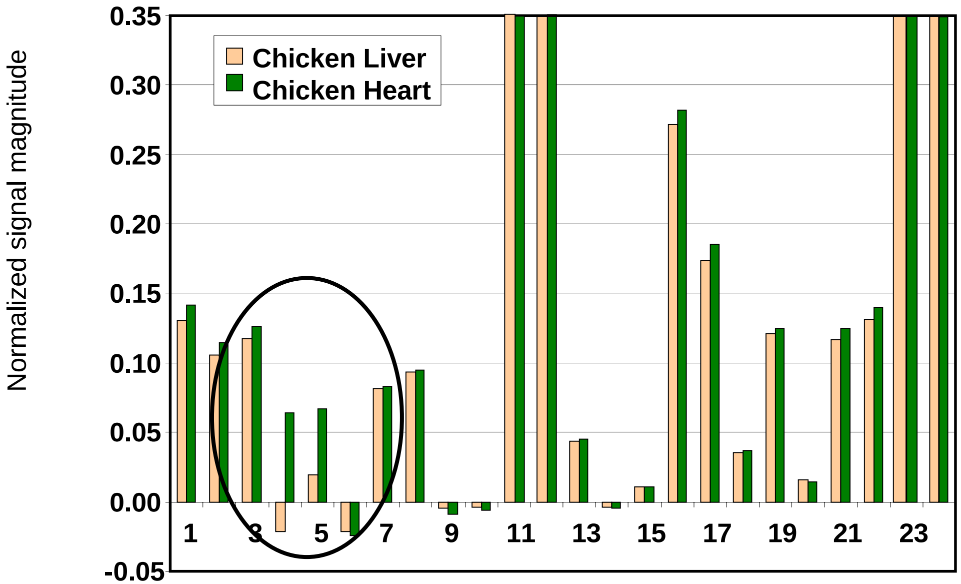




Variation 18%

Chicken liver versus muscle





Array variation
19%

Discussion

Otolaryngology–Head and Neck Surgery (2007) 137, 269-273

ORIGINAL RESEARCH

In vitro discrimination of tumor cell lines with an electronic nose

Kristin B. Gendron, MD, Neil G. Hockstein, MD, Erica R. Thaler, MD, Anil Vachani, MD, and **C. William Hanson, MD,** Philadelphia, PA

Adenocarcinoma, squamous, mesothelioma, fibroblasts, smooth muscle cells were distinguishable.

Conclusions

- 1) Media has a distinct fingerprint
- 2)Tumor types have distinct Enose signatures
- 3) Gross tissues can be differentiated

Future studies

- Confirm these preliminary findings
- If different types of cells can be distinguished, what is the cause of the difference?
- Develop this as a surgical tool
- Develop the Enose as a diagnostic tool that may allow further classification of pathological tissues such as tumors

Algorithms for Planning for Pediatric Neurosurgery

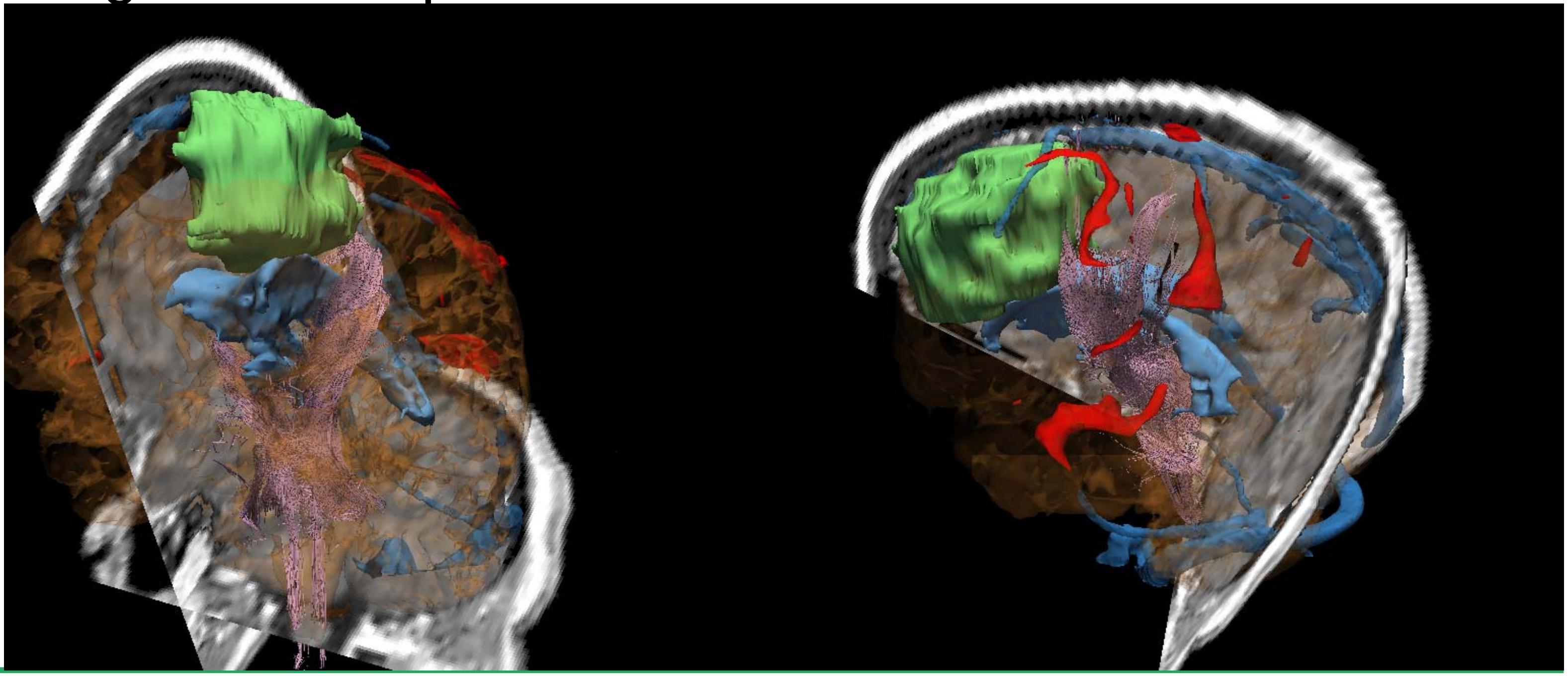
Simon K. Warfield, Ph.D.
Associate Professor of Radiology
Department of Radiology
Children’s Hospital Boston

Technology Guided Interventions

- Algorithms enable quantitative assessment and visualization:
  - segmentation
  - registration
  - validation.
- Illustrative application to image guided neurosurgery:
  - Preoperative surgical planning.
  - Intraoperative targeting and control.
  - Postoperative assessment.

Augmented Visualization

- Acquire MRI, DT-MRI, fMRI preoperatively
  - Plan intervention
  - Enhance tumor visualization
  - Better perceive critical healthy structures
- Align preoperative data with intraoperative configuration of patient

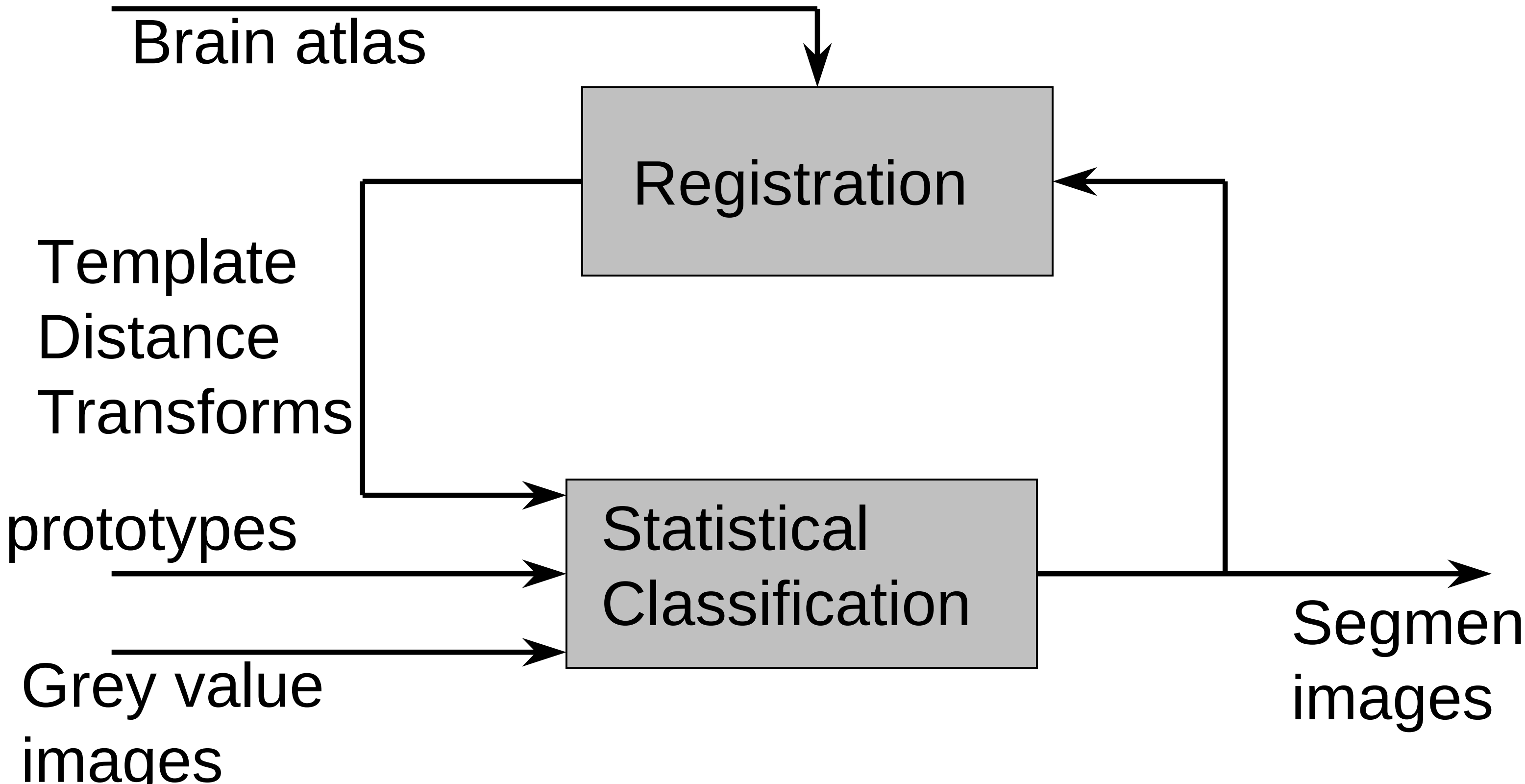


Segmentation

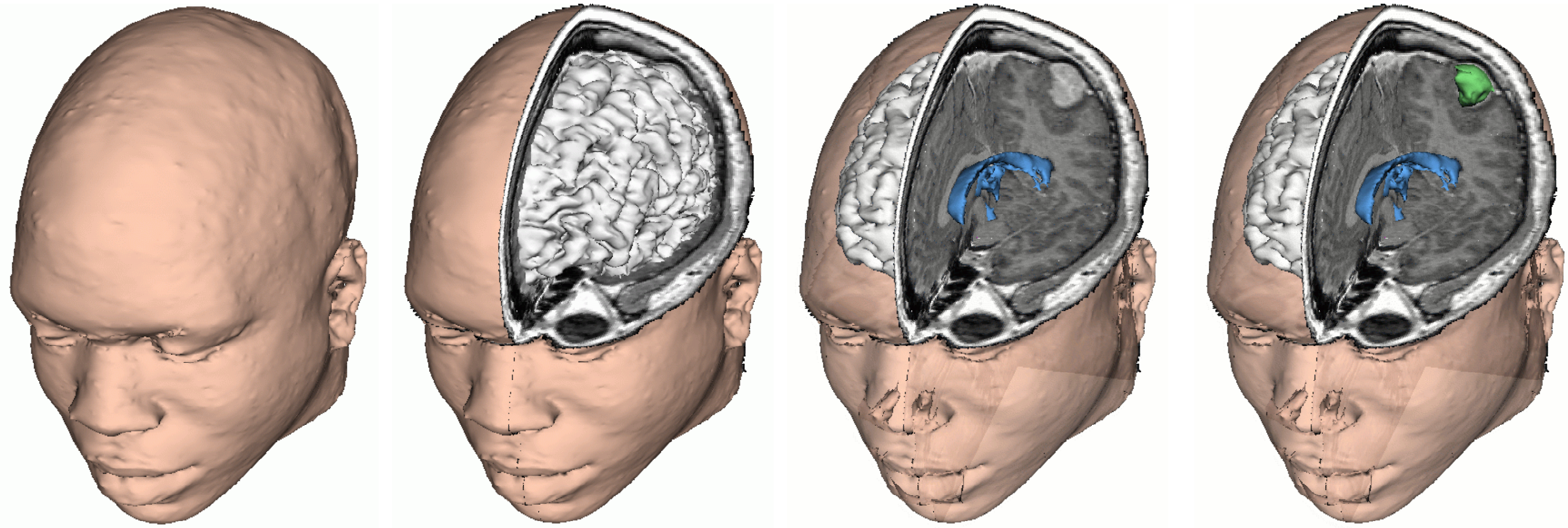
- Goal: identify or label structures present in the image.
- Wide range of techniques:
  - Interactive or manual delineation
  - Supervised approaches with user initialization
  - Alignment with a template
  - Statistical pattern recognition
- Applications:
  - Quantitative measurement of volume, shape or location of structures
  - Provides boundary for visualization by surface rendering

Segmentation

Combine statistical classification and registration of a digital anatomical atlas



Hierarchical Control Strategy



Skin Brain Ventricles Tumor

Validation of Image Segmentation

- Segmentation critical for preoperative planning, intraoperative targeting, and postoperative assessment.
- STAPLE (Simultaneous Truth and Performance Level Estimation):
  - An algorithm for estimating performance and ground truth from a collection of independent segmentations.
  - Warfield, Zou, Wells MICCAI 2002.
  - Warfield, Zou, Wells, IEEE TMI 2004.

Validation of Image Segmentation

- Spectrum of accuracy versus realism in reference standard.
- Digital phantoms.
  - Ground truth known accurately.
  - Not so realistic.
- Acquisitions and careful segmentation.
  - Some uncertainty in ground truth.
  - More realistic.
- Autopsy/histopathology.
  - Addresses pathology directly; resolution.
- Clinical data ?
  - Hard to know ground truth.
  - Most realistic model.

Validation of Image Segmentation

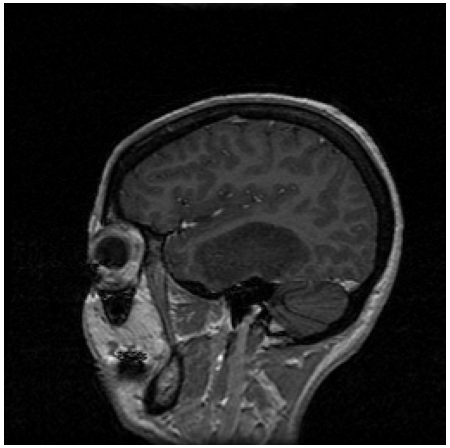
- Comparison to expert performance; to other algorithms:
  - What is the appropriate measure for such comparisons ?
- Our new approach:
  - Simultaneous estimation of hidden ``ground truth'' and expert performance.
  - Enables comparison between and to experts.
  - Can be easily applied to clinical data exhibiting range of normal and pathological variability.

Estimation Problem

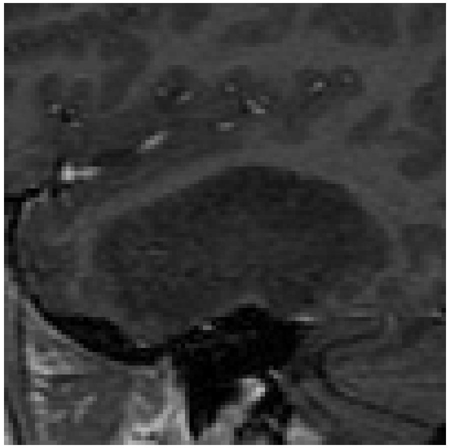
- Complete data density: $f(\mathbf{D},\mathbf{T}\,|\,\mathbf{p},\mathbf{q})$
    - Binary ground truth T_i for each voxel i.
    - Expert j makes segmentation decisions $D_{ij.}$
    - Expert performance characterized by sensitivity p and specificity q.
  - We observe expert decisions **D**. If we knew ground truth **T**, we could construct maximum likelihood estimates for each expert's sensitivity (true positive fraction) and specificity (true negative fraction):

$$\hat{\mathbf{p}},\hat{\mathbf{q}} = \arg\max_{\mathbf{p},\mathbf{q}} \ln f(\mathbf{D},\mathbf{T}\,|\,\mathbf{p},\mathbf{q})$$

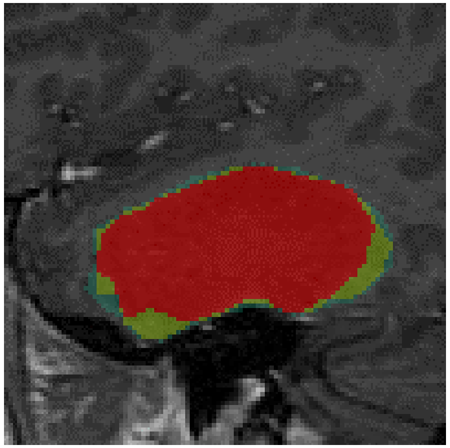
Tumor Segmentation Evaluation



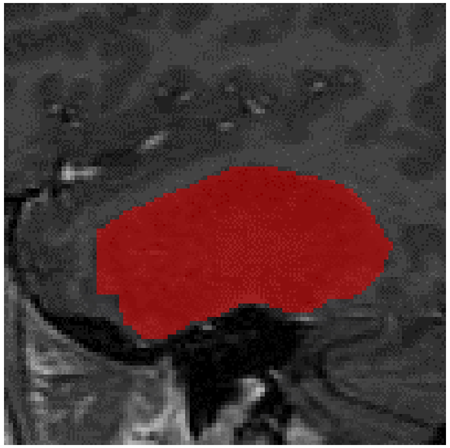
MR image



Tumor region



Experts



STAPLE

	1	2	3	auto
p_j	0.8951	0.9993	0.9986	0.9063
q_j	0.9999	0.9857	0.9982	0.9990

Registration

- Goal: Bring image acquisitions into alignment
- Intra-subject
  - Fuse multiple modalities
  - Improve segmentation by using multiple contrast mechanisms
  - Enhance visualization by overlap or blending different data
  - Capture soft tissue deformation
- Inter-subject
  - ``atlasing'' - compare groups

Targeting in Neurosurgery

- Capturing brain deformation.
  - Intraoperative **nonrigid** registration.

- Warfield et al. Med Imag Anal 2005.
- Clatz et al. IEEE TMI 2005.
- Archip et al. NeuroImage 2007

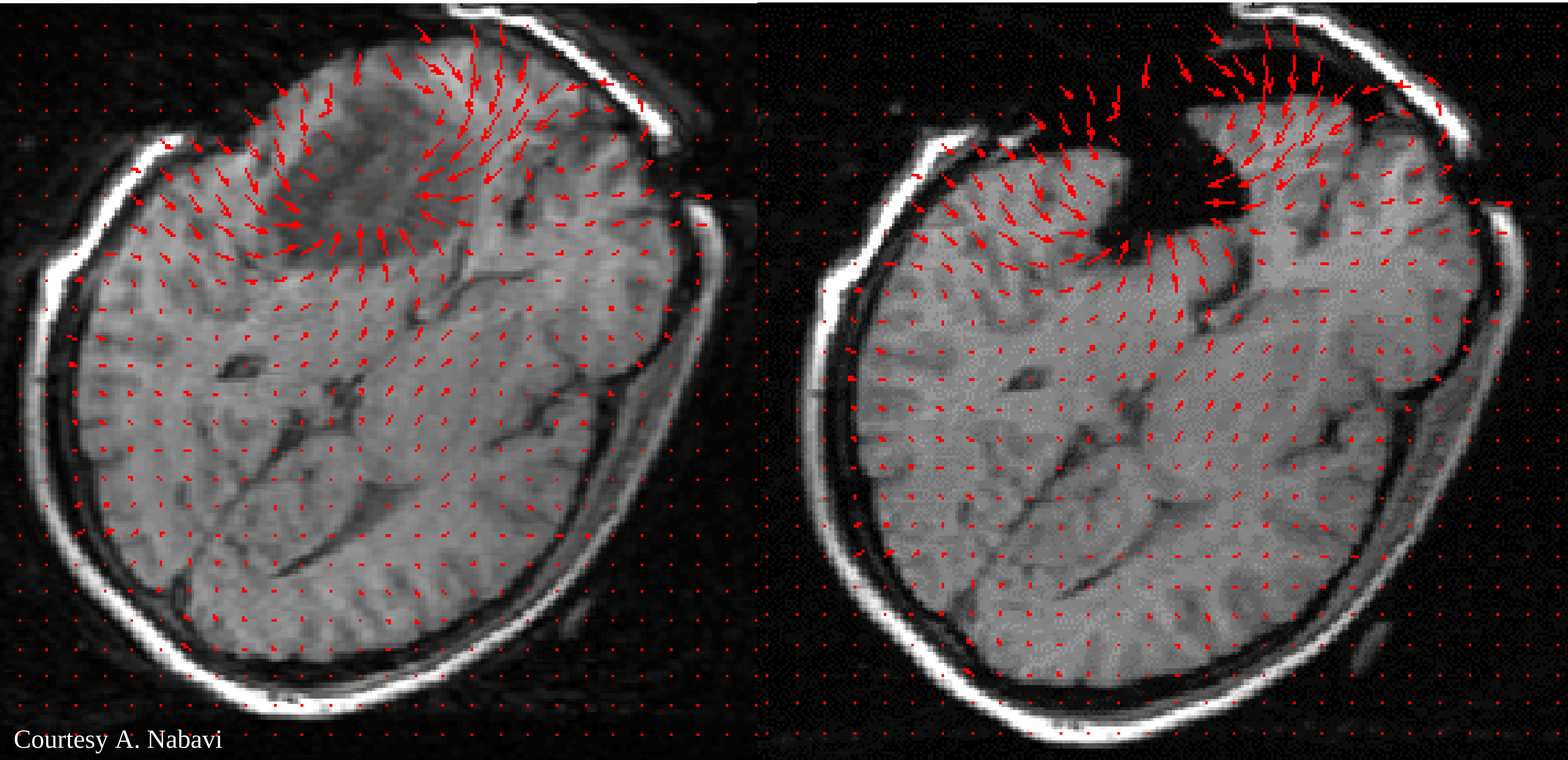
Intra-operative MRI

Open configuration MR scanner

Operating Room

“Brain Shift” happens

- Nabavi et al. Neurosurgery 2001

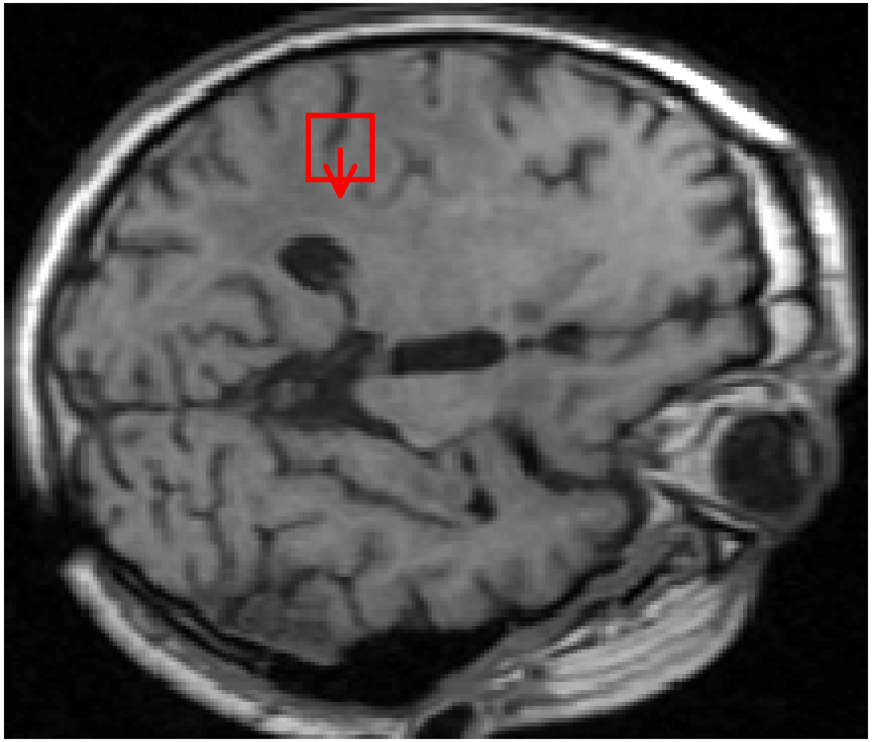


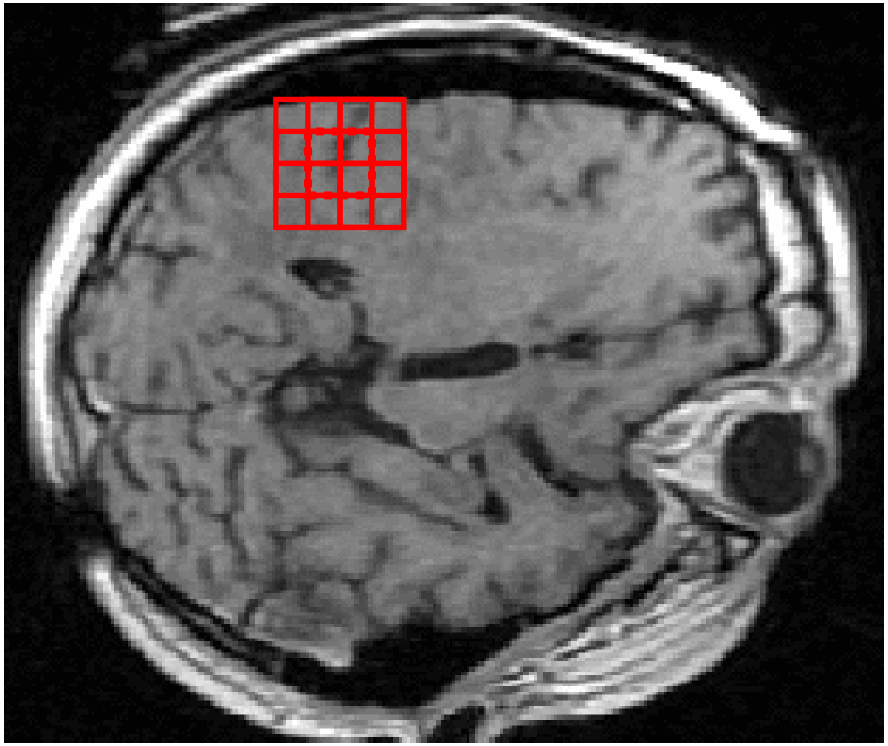
Courtesy A. Nabavi

Intraoperative Nonrigid Registration

- **Fast:** it should not take more than 1 min to make the registration.
- **Robust:** the registration should work with poor quality image, artifacts, tumor...
- **Physics based:** we are not only concerned in the intensity matching, but also interested in recovering the physical (mechanical) deformation of the brain.
- **Accurate:** neuro-surgery needs a precise knowledge of the position of the structures.

Block Matching Algorithm



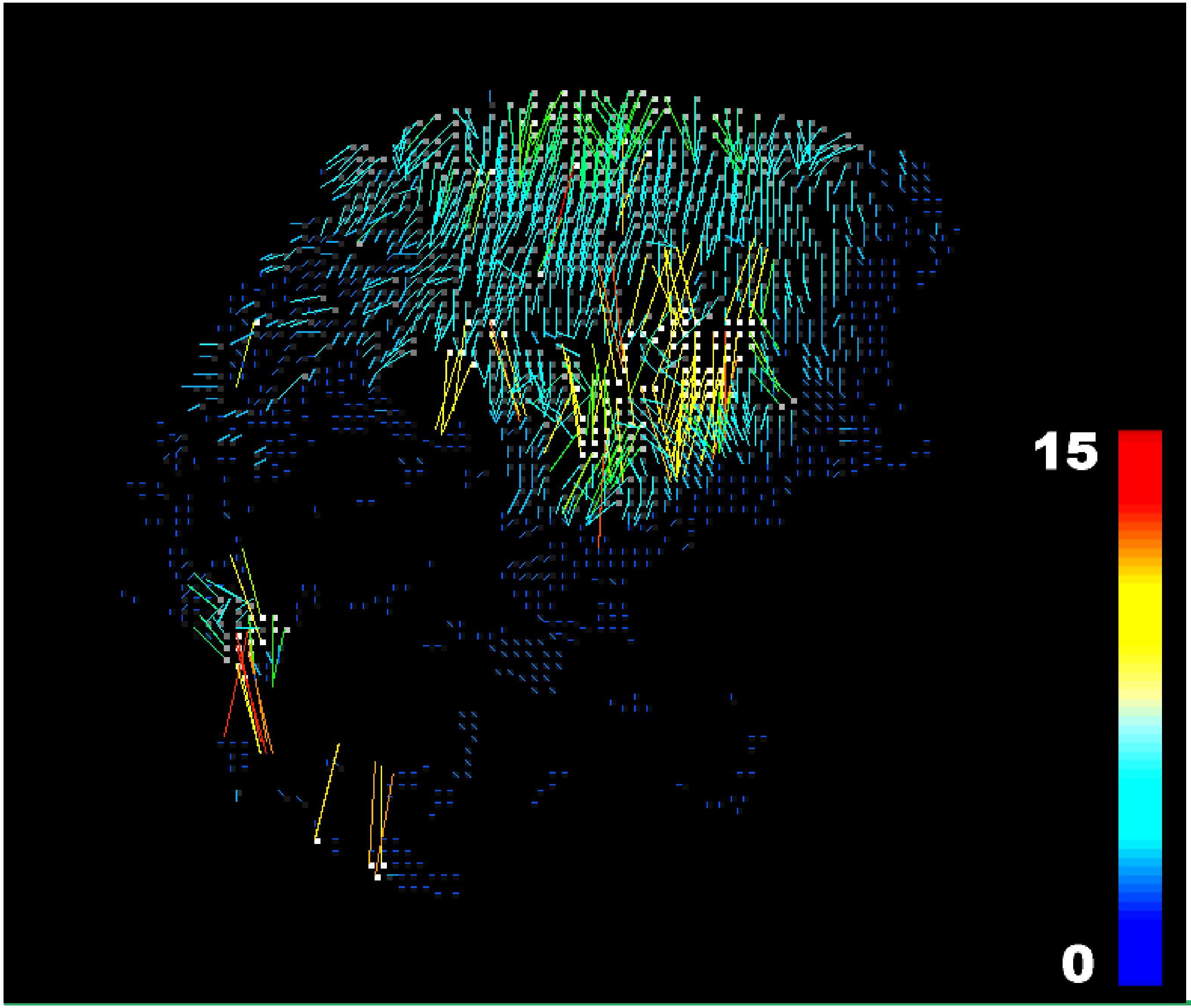


Similarity measure: coefficient of correlation $\in [0:1]$

Divide a global optimization problem in many simple local ones

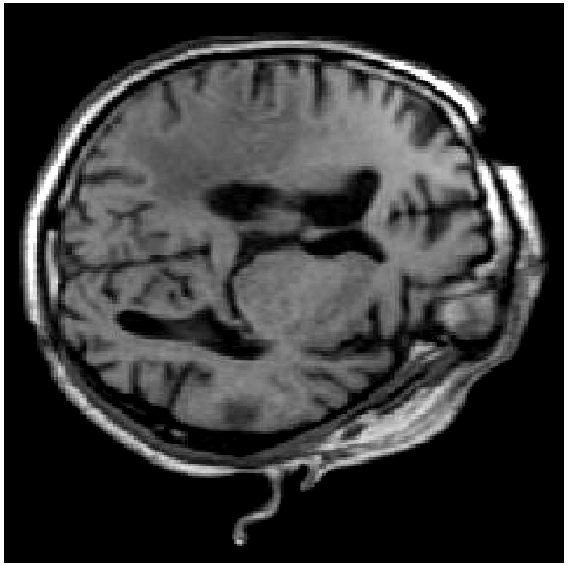
Highly parallelizable, as blocks can be matched independently.

Block Matching Algorithm

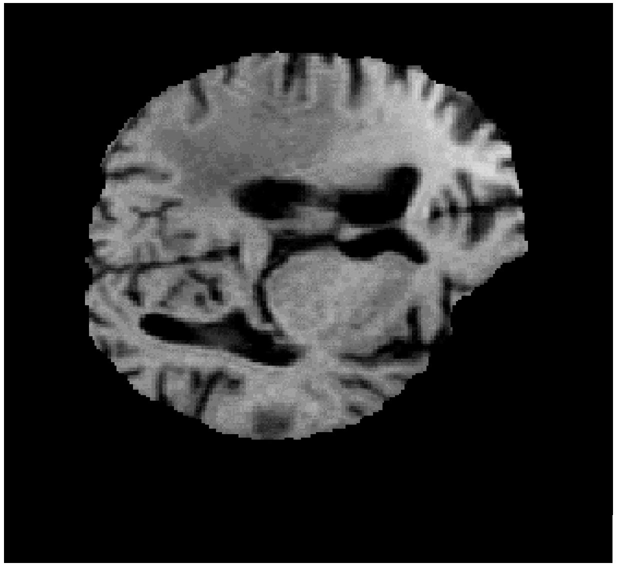


Displacement estimates are noisy.

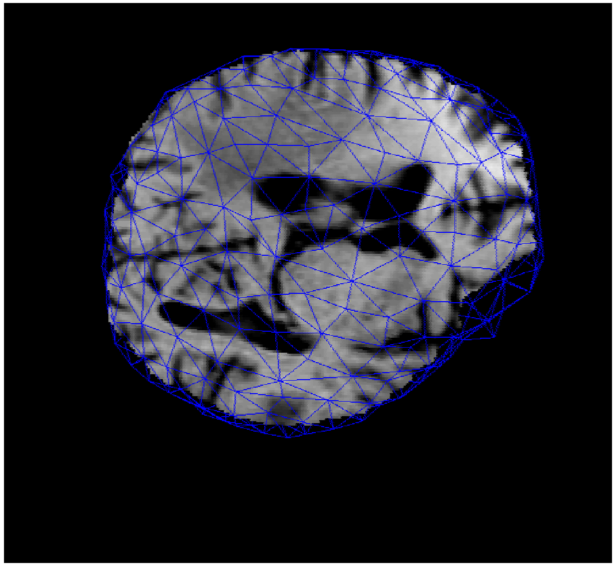
Patient-specific Biomechanical Model



Pre-operative image



Automatic brain segmentation



Brain finite element model (linear elastic)

Registration Formulation

- Approximation: robust but not accurate
- Interpolation: accurate but not robust

Solution: Iterative strategy shifting from approximating to interpolating:

+ Use the mechanical knowledge introduced by the approximation to select physically realistic matches.

+ Converge to the interpolation while increasingly trusting the remaining matches.

Gradual Approach

Method: iterative method introducing an external force F balancing the mesh internal mechanical energy:

$$\left[K + H^{T}SH\right]U = H^{T}SD + F$$

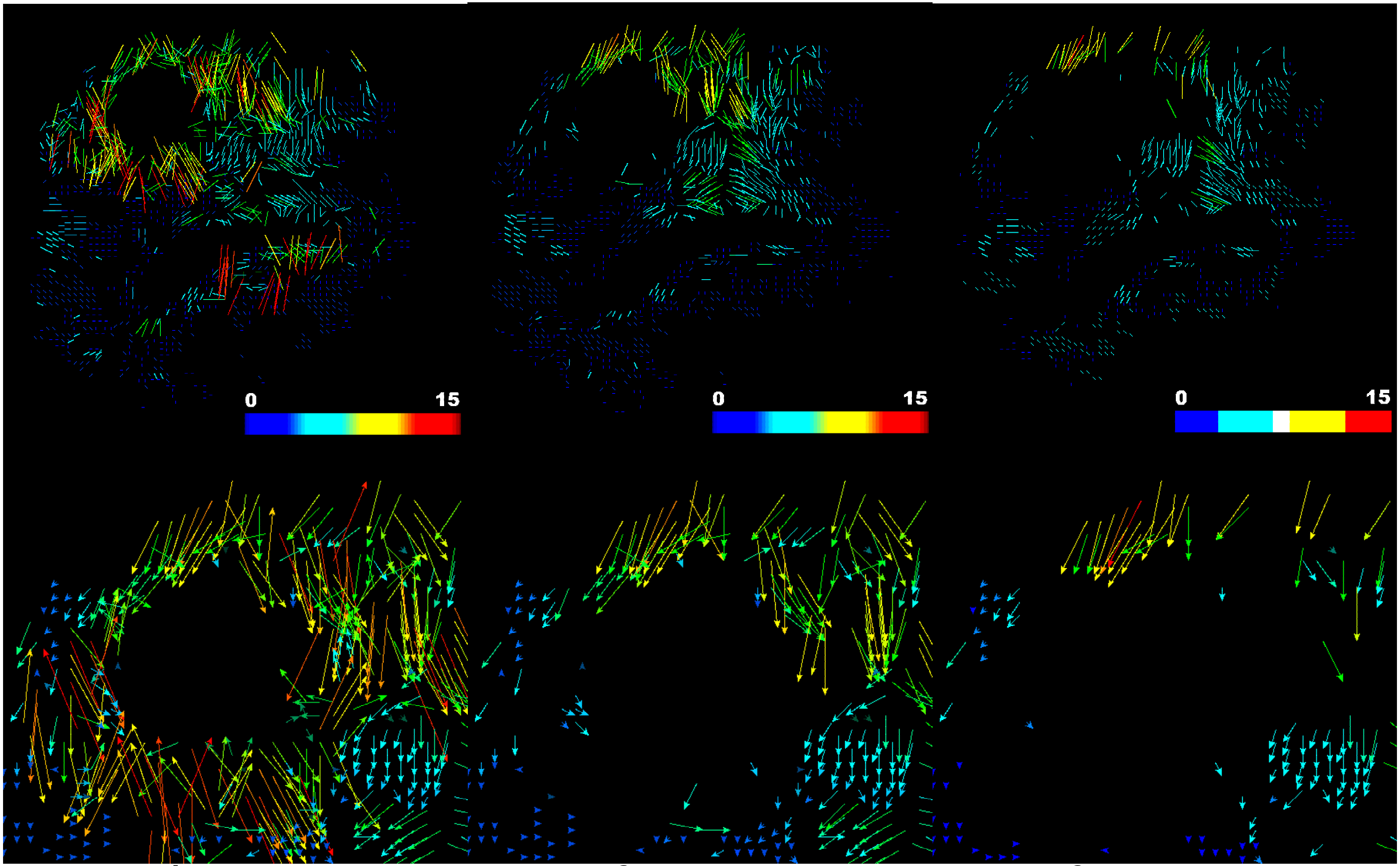
Algorithm:

$$F_i \Leftarrow KU_i$$

$$U_{i+1} \Leftarrow \left[K + H^{T}SH\right]^{-1}\left[H^{T}SD + F_i\right]$$

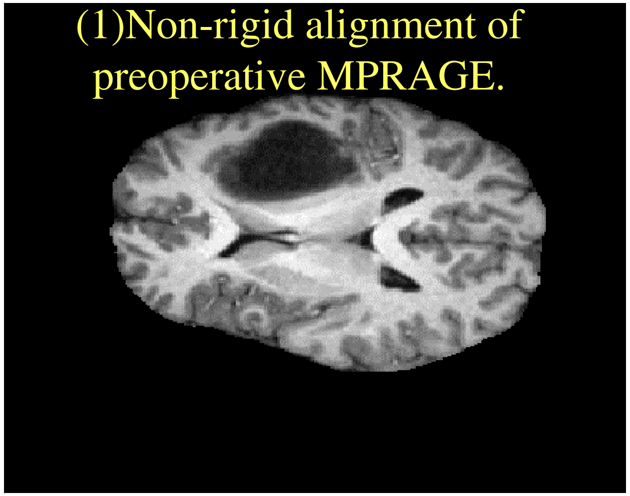
At each iteration, reject % of outliers based on a least trimmed squared algorithm.

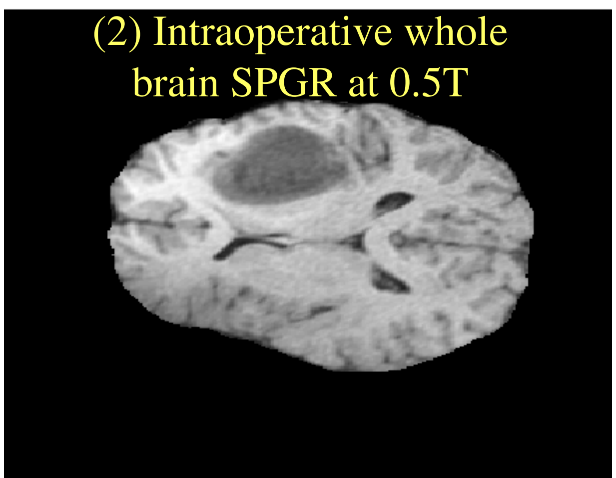
Gradual Approach

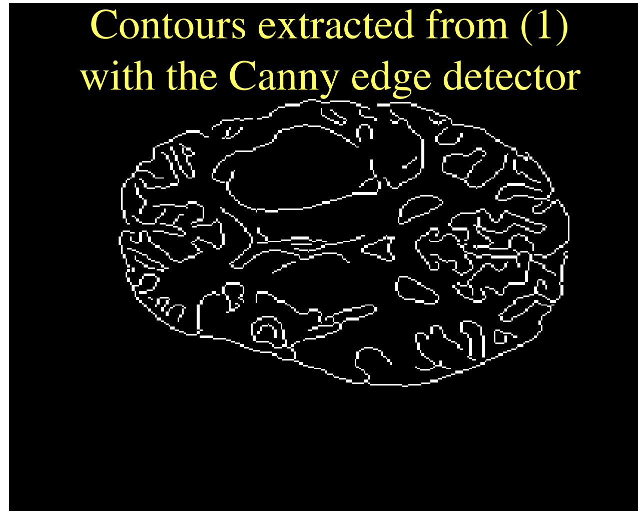


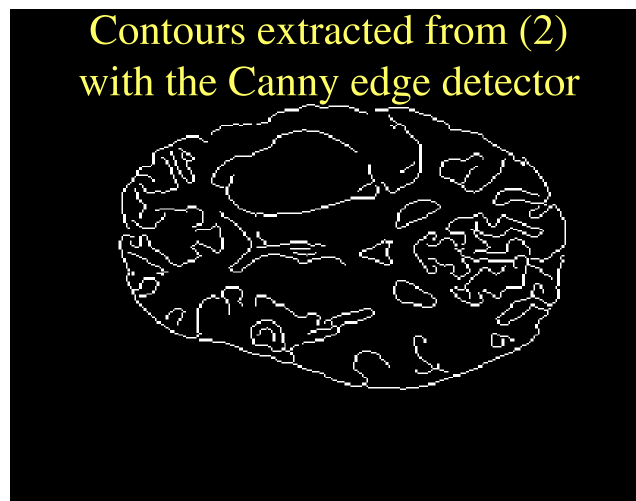
First step After 5 steps After 10 steps

Registration accuracy









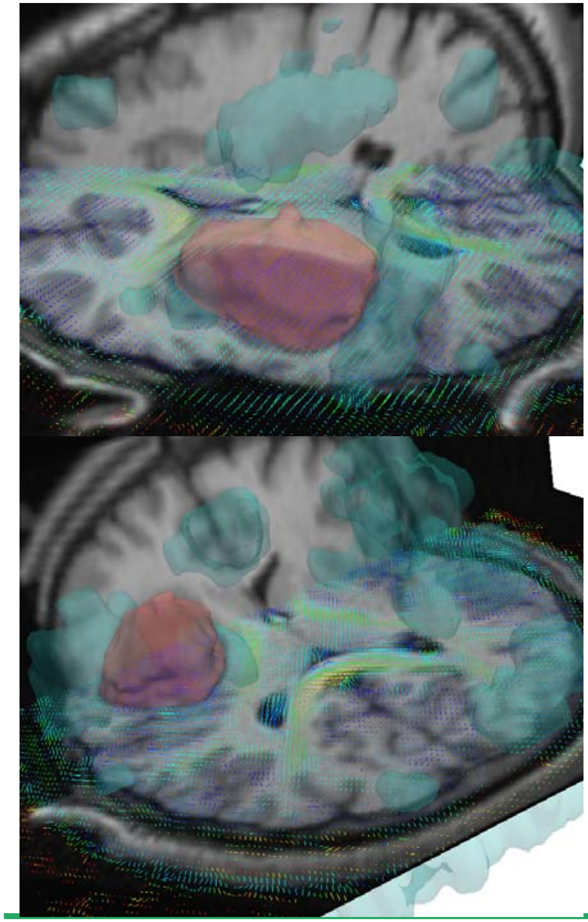
95% Hausdorff metric computed

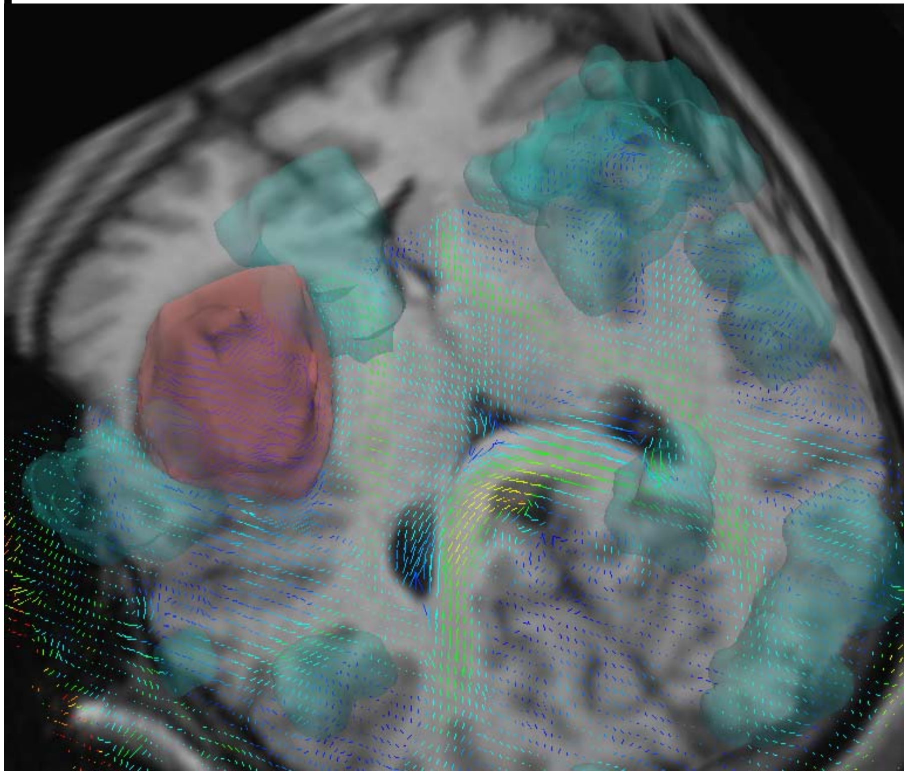
Results

	Tumor position	Tumor pathology	Non-rigid registration – preop to intraop scans (95% Hausdorff distance)			
			Max Displacement measured (mm)	Rigid registration accuracy – preop to intraop (mm)	Non-Rigid registration accuracy – preop to intraop (mm)	Ratio Rigid/Non-Rigid
Case 1	right posterior frontal	oligoastrocytoma Grade II	10.68	5.95	1.90	3.13
Case 2	left posterior temporal	glioblastoma Grade IV	21.03	10.71	2.90	3.69
Case 3	left medial temporal	glioblastoma Grade IV	15.27	7.65	1.70	4.50
Case 4	left temporal	anaplastic oligoastrocytoma Grade III	10.00	6.80	0.85	8.00
Case 5	right frontal	oligoastrocytoma Grade II	9.87	5.10	1.27	4.01
Case 6	left frontal	anaplastic astrocytoma Grade III	17.48	10.20	3.57	2.85
Case 7	right medial temporal	anaplastic astrocytoma Grade III	19.96	9.35	2.55	3.66
Case 8	right frontal	oligoastrocytoma Grade II	17.44	8.33	1.19	7.00
Case 9	right frontotemporal	oligoastrocytoma Grade II	15.08	7.14	1.87	3.81
Case 10	right occipital	anaplastic oligodendroglioma Grade III	9.48	5.95	1.44	4.13
Case 11	left frontotemporal	oligodendroglioma Grade II	10.74	4.76	0.85	5.60
AVG			**14.27**	**7.44**	**1.82**	**4.58**

Results

- Matched preoperative fMRI and DT-MRI aligned with intraoperative MRI.

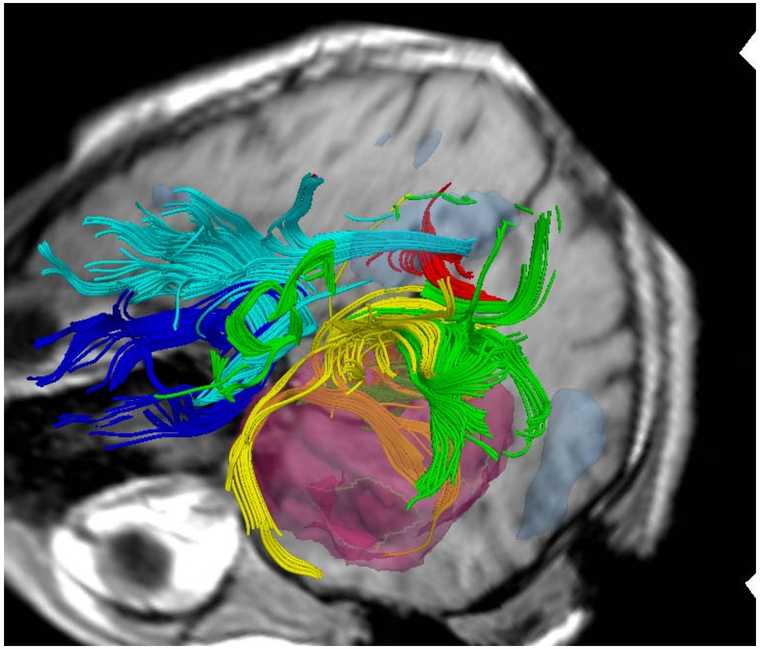


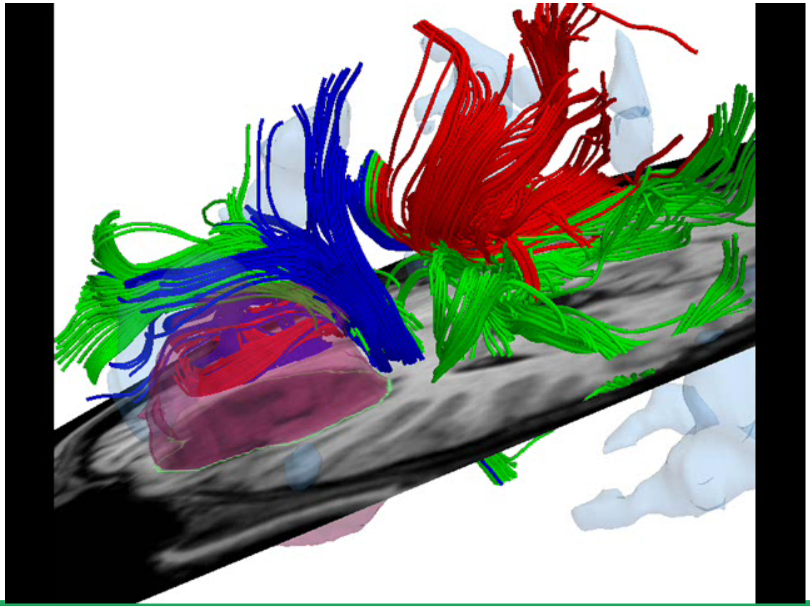


Tensor alignment: Ruiz et al. 2000

Results

- Alignment of pre-operative data to the intra-operative images was achieved during the neurosurgery.





Conclusion

- Planning, targeting and intervention in surgical procedures augmented through algorithms for:
- Visualization
  - Requires segmentation to identify structures for rendering
- Segmentation
  - Validation of segmentation with STAPLE
- Registration
  - Real-time nonrigid registration during surgery

Acknowledgements

Colleagues contributing to this work:

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- Karol Miller.
- Liliana Goumnerova.
- Blaise Bourgeois.
- Frank Duffy.
- Arne Hans.
- Olivier Clatz.

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NSF ITR

R01 RR021885

A CASE REPORT: Tumefactive Multiple Sclerosis: Comparative Imaging Techniques

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The George Washington University
School of Medicine
Washington, DC

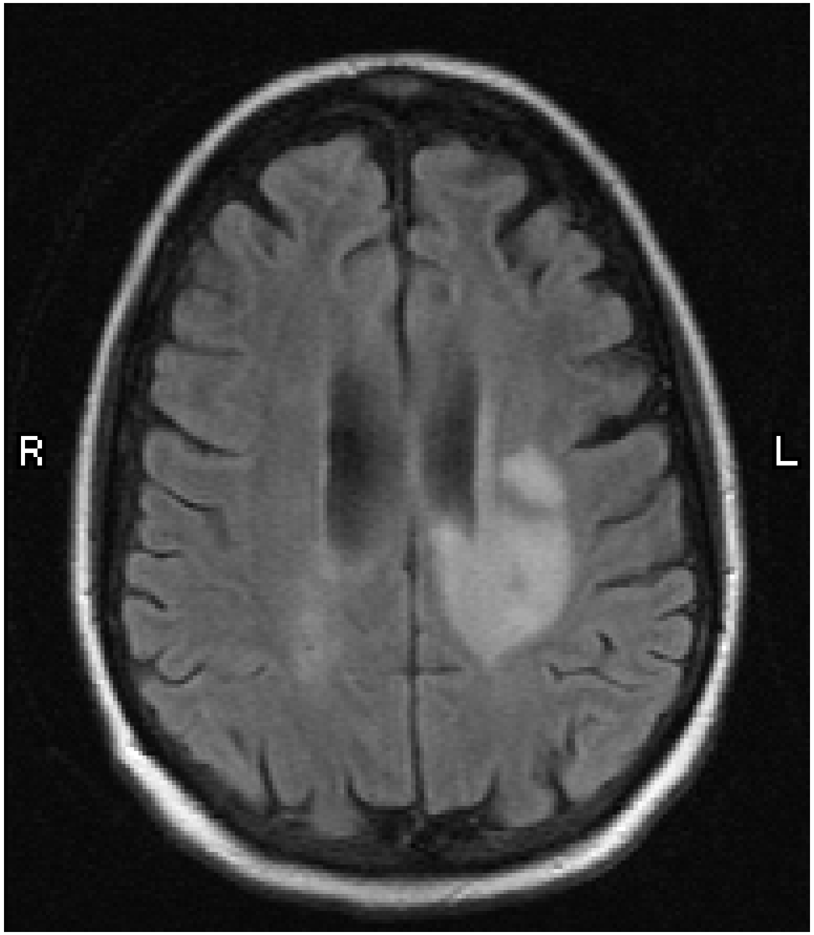
Case Report

- CC: balance trouble
- HPI: 56-year-old woman, walking difficulty 9/06 diagnosed elsewhere as MS. Per report positive MRI brain and positive LP. Since then on intramuscular IFN-beta1a weekly.
- 7 months later progressive BLE weakness and imbalance over 1 week
- Denied visual sx, numbness, bowel/bladder sx, fever, recent illness or immunization

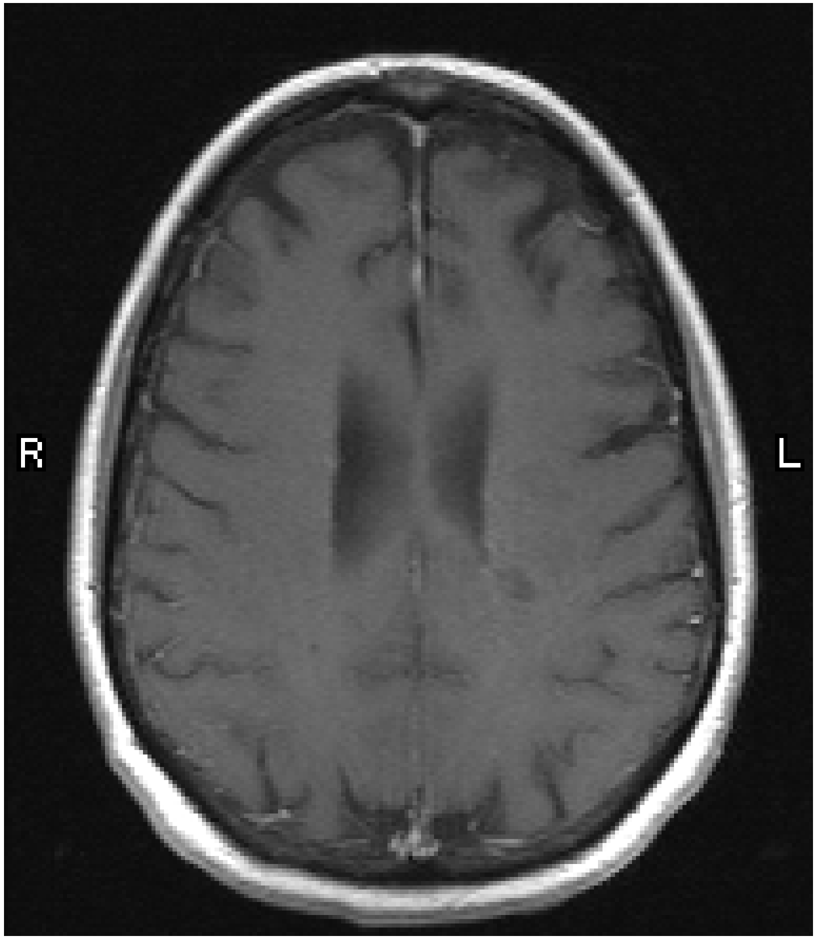
History and Physical

- PMHx:
  - MS, dx 9/2006
  - Hypothyroidism
  - Migraine headaches
  - Depression
  - Hypertension
- Meds:
  - IFN-beta1a, thyroxine, metoprolol, simvastatin, valproate
- FMH/SOC: negative
- PE:
  - Motor: 4+/5 weakness left arm and leg, increased tone in left leg
  - DTR: brisk, symmetric; bilateral Babinski signs
  - Sens: normal
  - Coord: left arm and leg dysmetria
  - Gait: ataxia

Diagnostic tests: MRI (09-06)

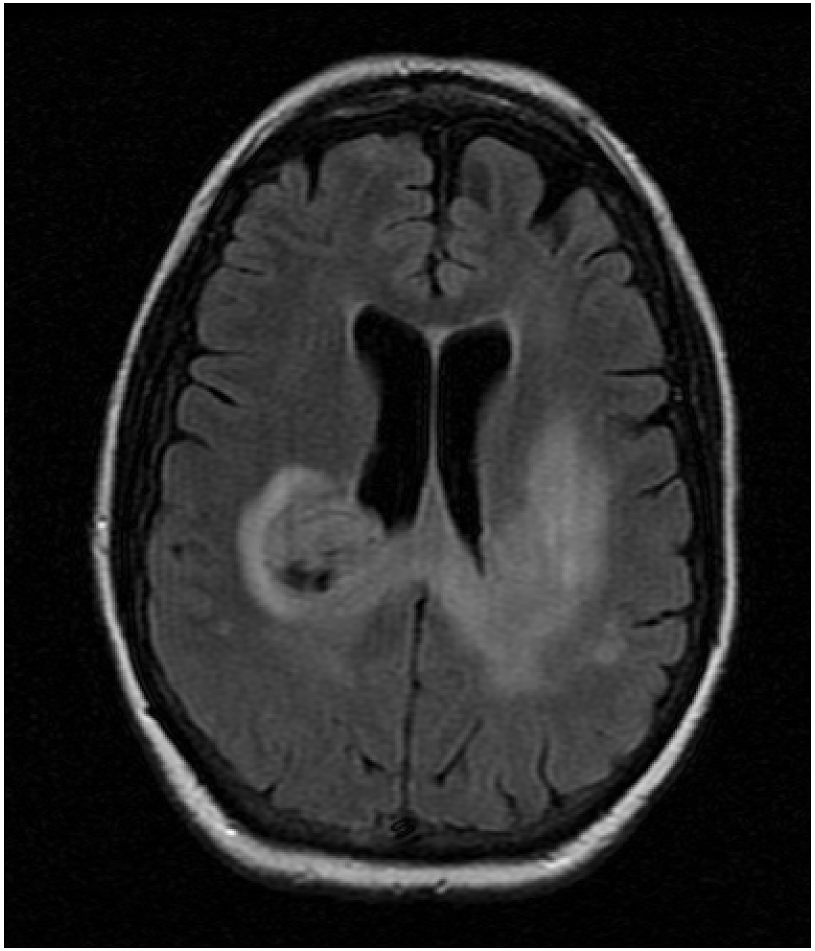


A. *FLAIR*

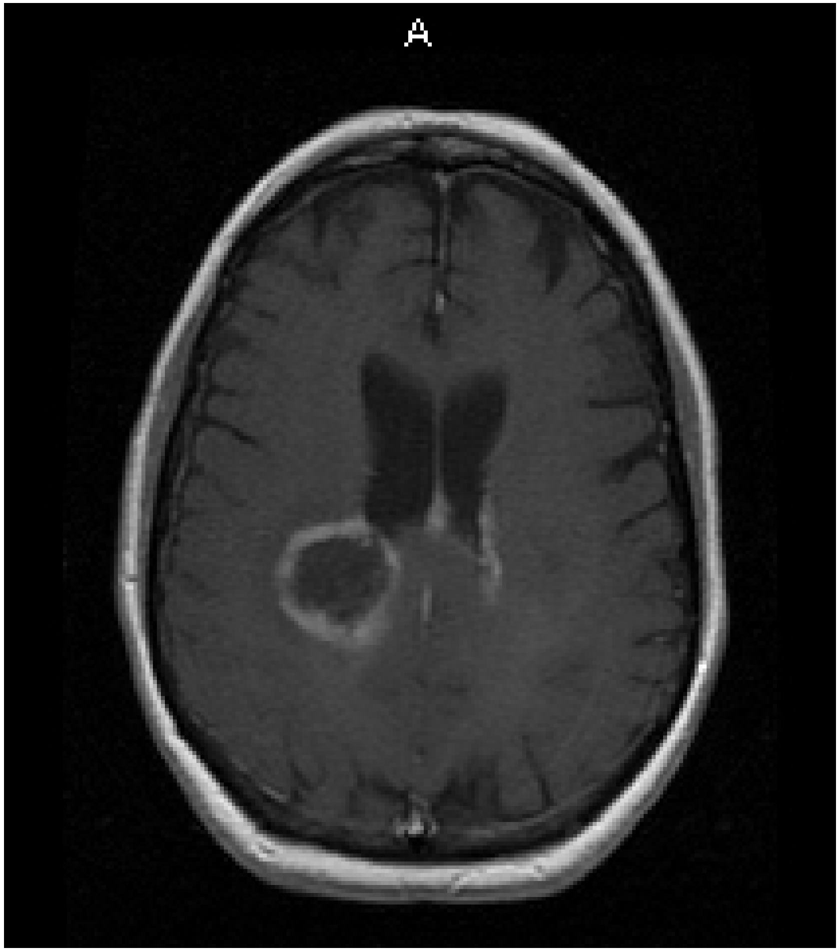


B. *T1-weighted with contrast*

Diagnostic tests: MRI (04-07)

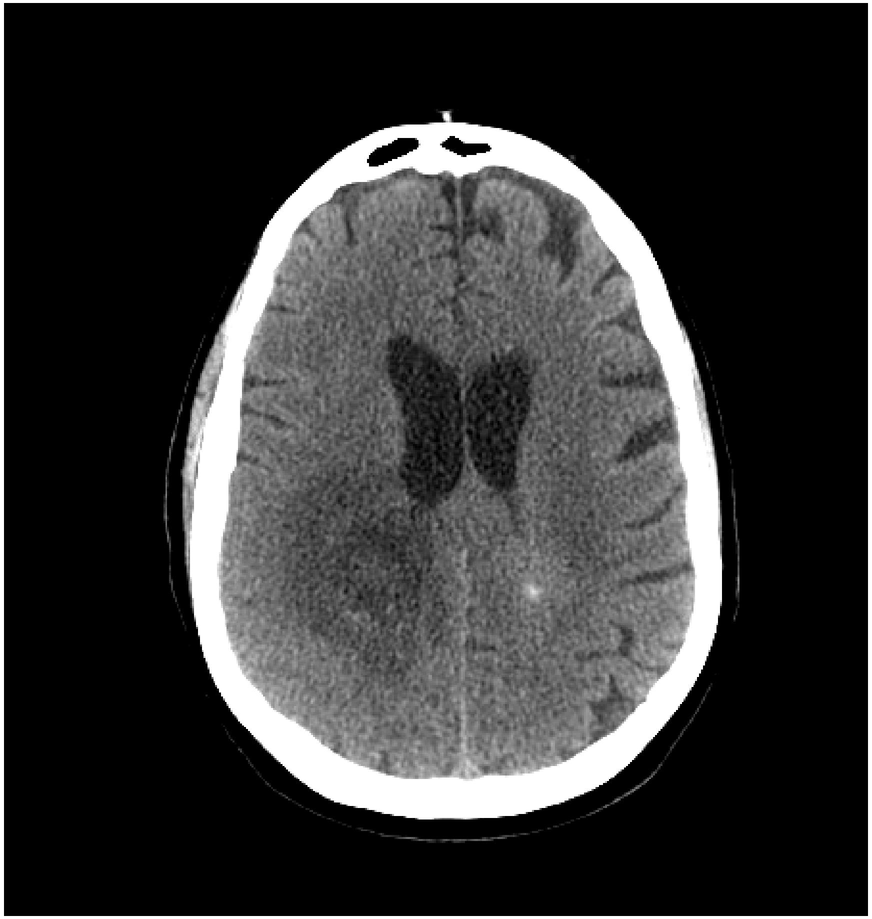


A. *FLAIR*



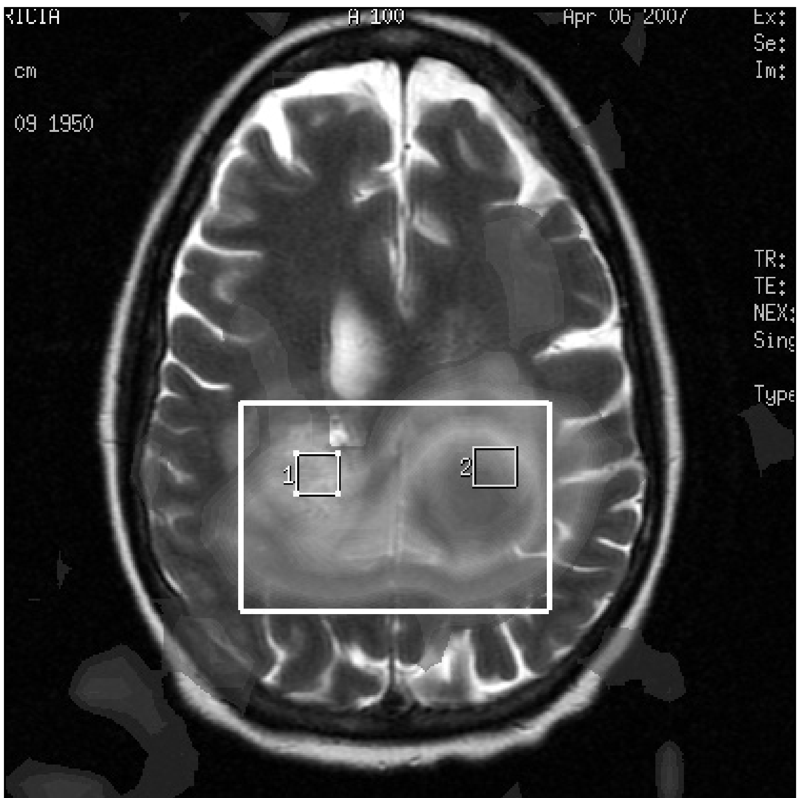
B. *T1-weighted with contrast*

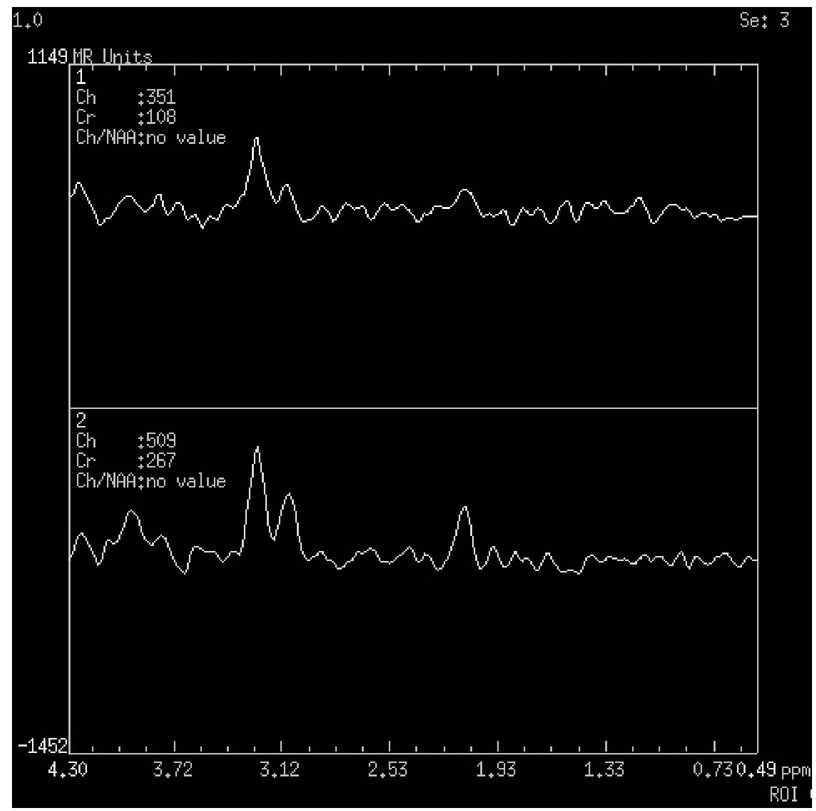
Diagnostic tests: CT (04-07)



Diagnostic tests: MRS (04-07)

reduced NAA/Cr in right-side lesion,
mild increased choline peak on left side

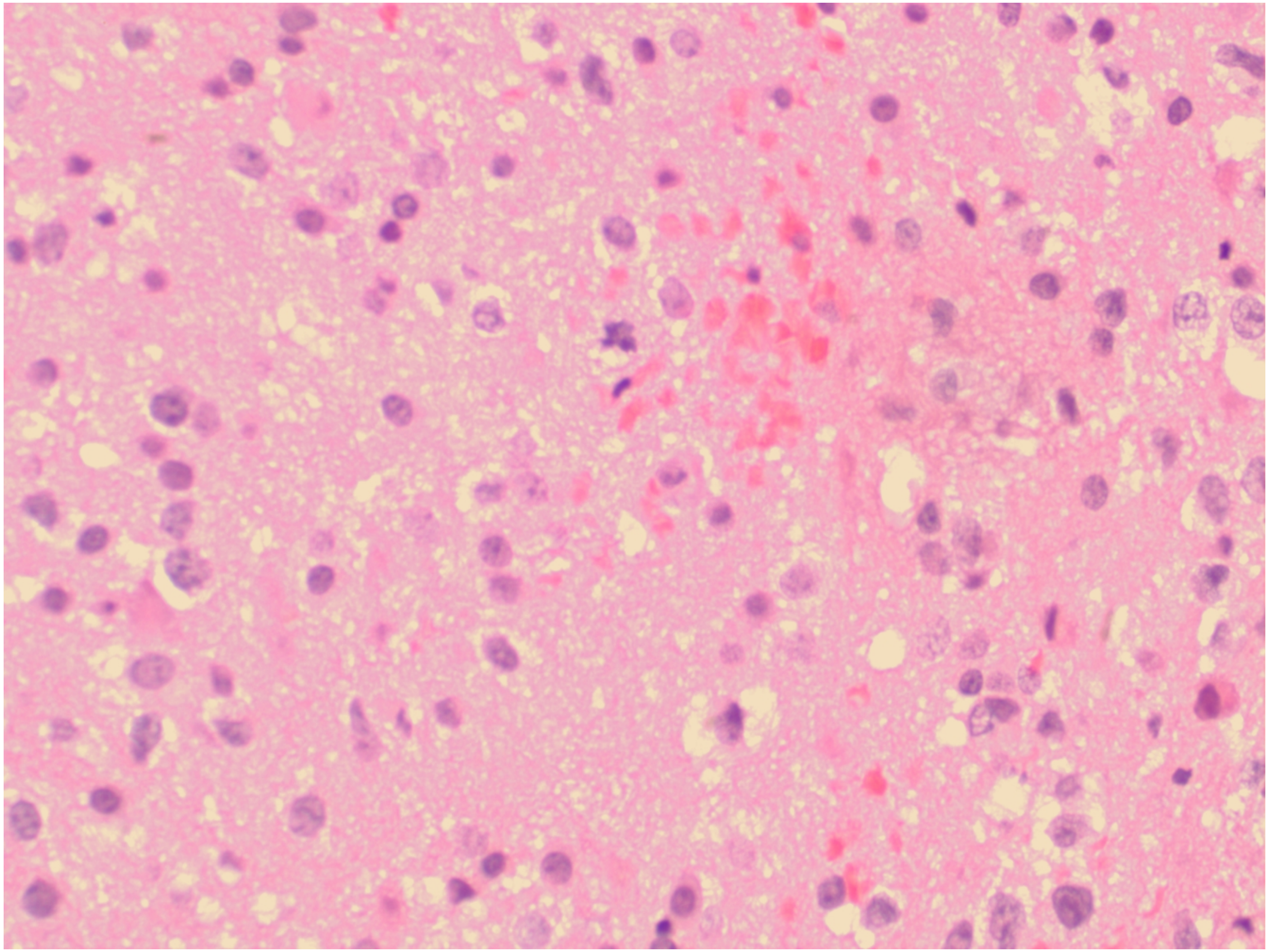




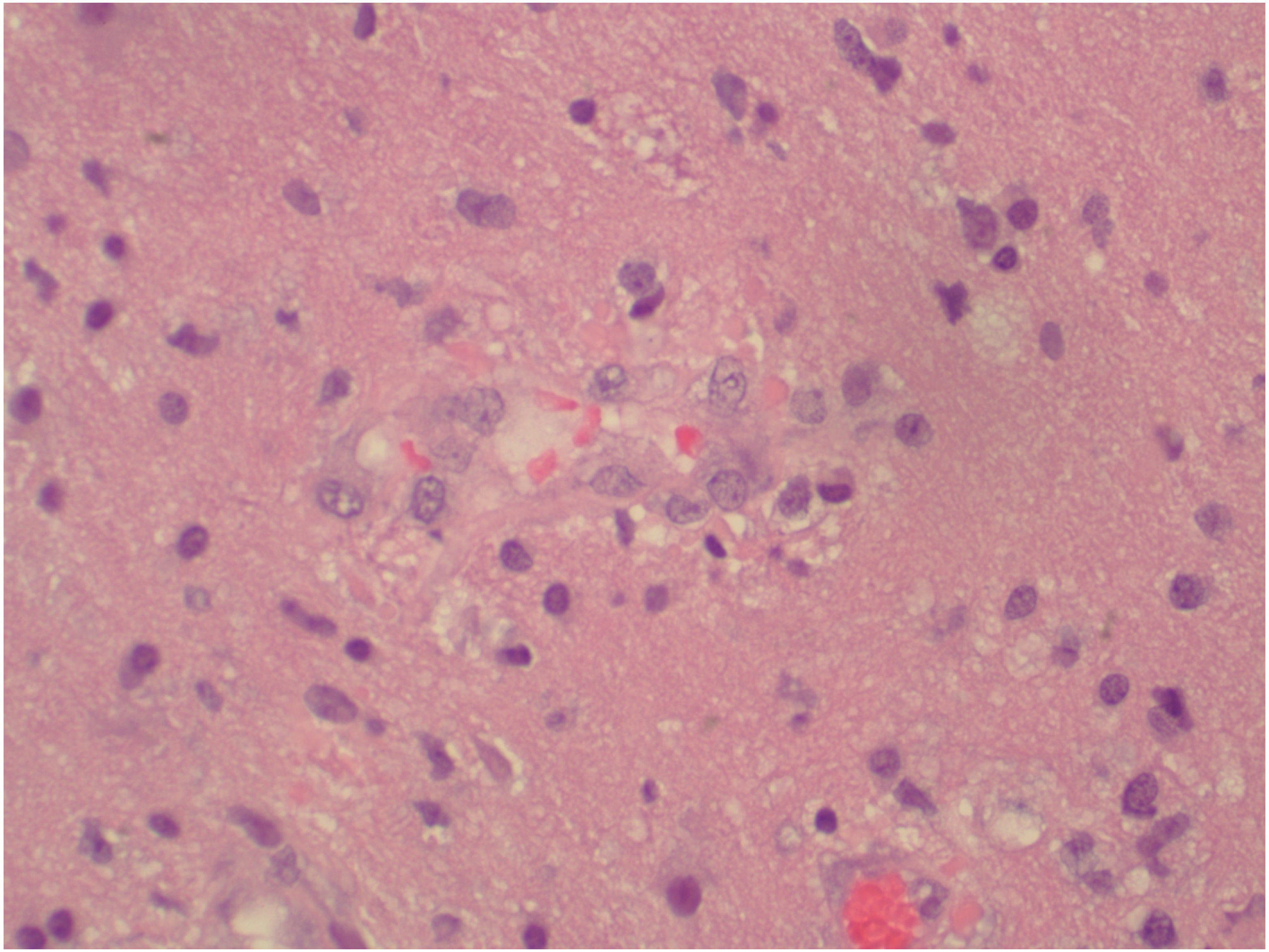
Hospital course

- CBC, chem, ESR, CRP, B12, Folate, HIV negative or normal
- MRI C-spine: normal
- initially started on Solumedrol 1gm IV 5 days for presumed MS exacerbation
- progressed to hemiplegia, delirium, agitation
- **brain biopsy**

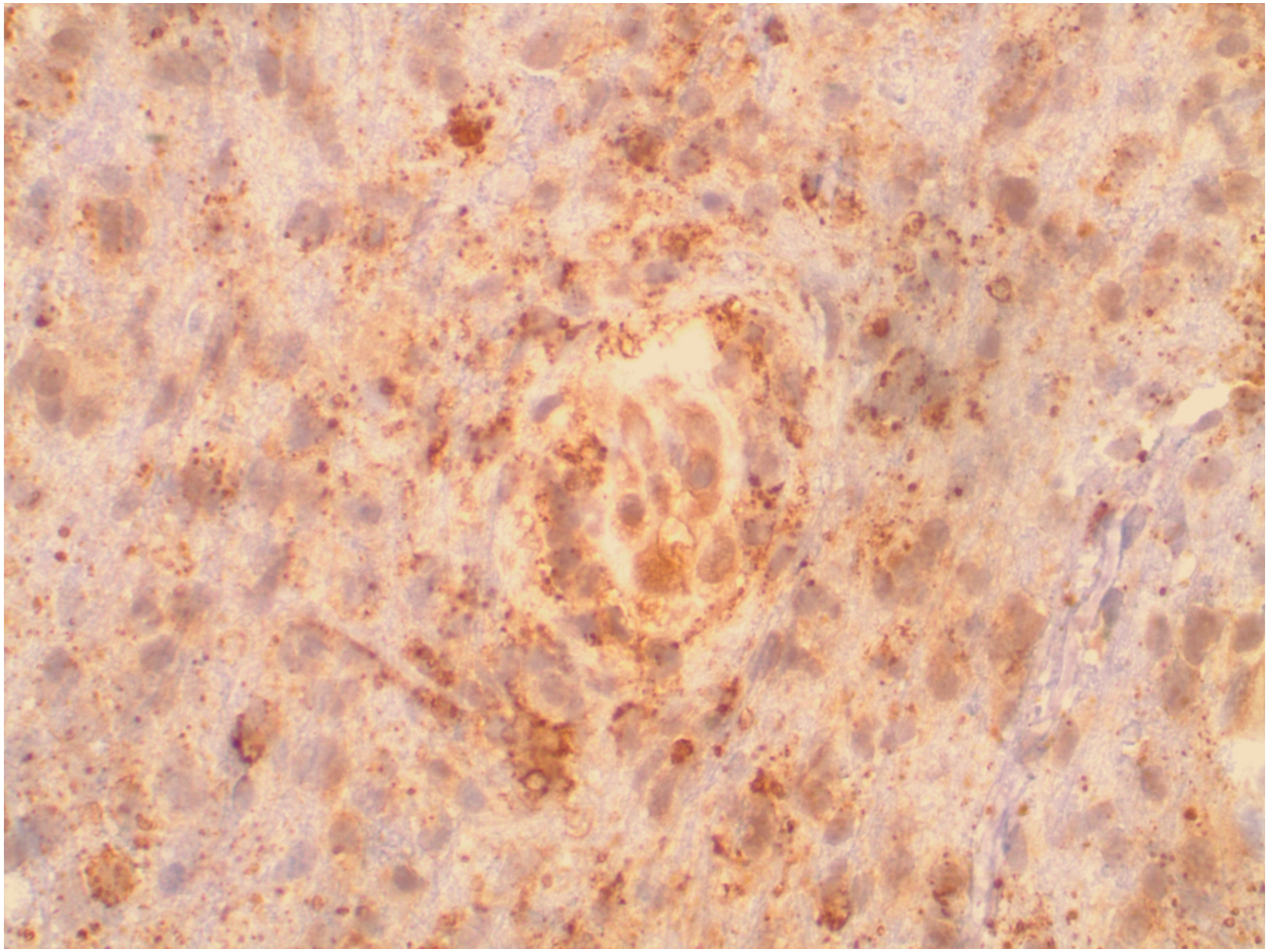
Pathology: H&E stain shows brain parenchyma with increased macrophages (identified by their clear cytoplasm)



Pathology: H&E stain shows macrophages around a blood vessel in the center of the field.



Pathology: CD68 immunostain (a marker for macrophages) highlights the macrophages especially around the central blood vessel



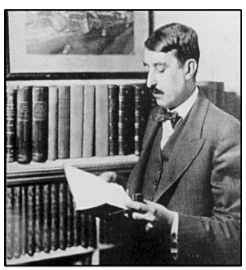
Differential Diagnosis

- neoplasm: glioma, metastases
- neoplasm: lymphoma
- cerebral abscess
- Progressive Multifocal Leukoencephalopathy
- Demyelinating disease:
  - Tumefactive MS – *only 1 prior case report of relapsing-remitting tumefactive MS*
    - Clinically isolated syndrome (CIS) vs. multiple sclerosis (MS)
  - Marburg variant - *encephalitis periaxialis scleroticans*
  - Balo's disease – *encephalitis periaxialis concentrica*
  - Schilder's disease – *encephalitis periaxialis diffusa*
  - ADEM – *acute disseminated encephalomyelitis (post-infectious/post-vaccinial)*
  - acute hemorrhagic leukoencephalitis
  - leukodystrophies – *adrenoleukodystrophy, metachromatic leukodystrophy*

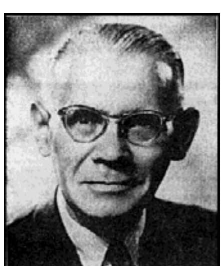
Poser, Clin Neurol Neurosurg 106 (2004) 159-171,
Selkirk, Mult Scler 11 (2005) 731-734

Atypical MS

Otto Marburg 1874-1948



Paul Schilder 1886-1940



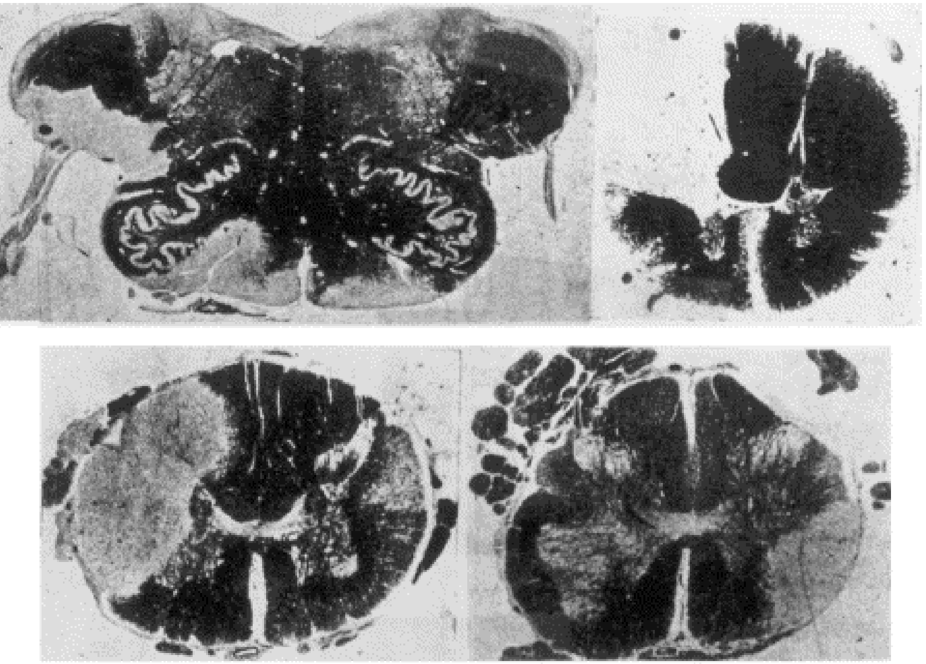
Joseph Baló 1895-1979

- **A.** Marburg variant - *encephalitis periaxialis scleroticans*
- **B.** Schilder’s disease - *encephalitis periaxialis diffusa*
- **C.** Balo’s disease - *encephalitis periaxialis concentrica*
- **D.** acute hemorrhagic leukoencephalitis
- **E.** ADEM – *acute disseminated encephalomyelitis*

Poser, Clin Neurol Neurosurg 106 (2004) 159-171

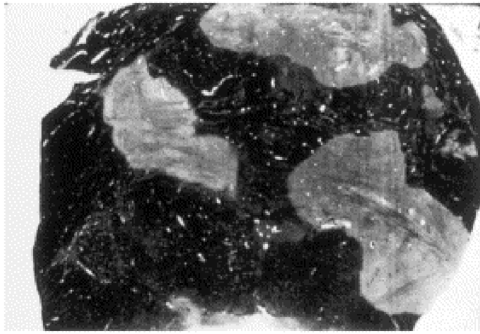
A

Marburg's Disease



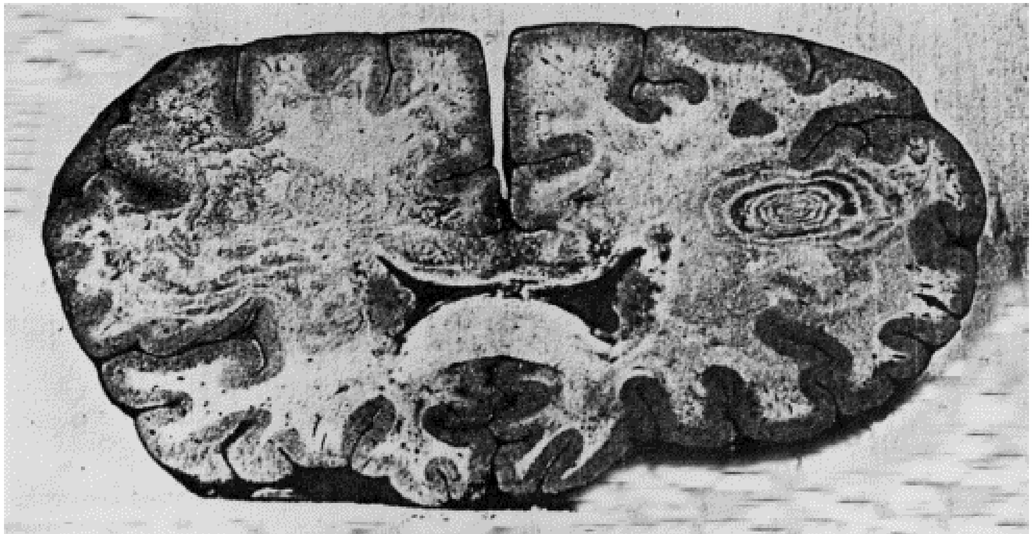
B

Schilder's Disease



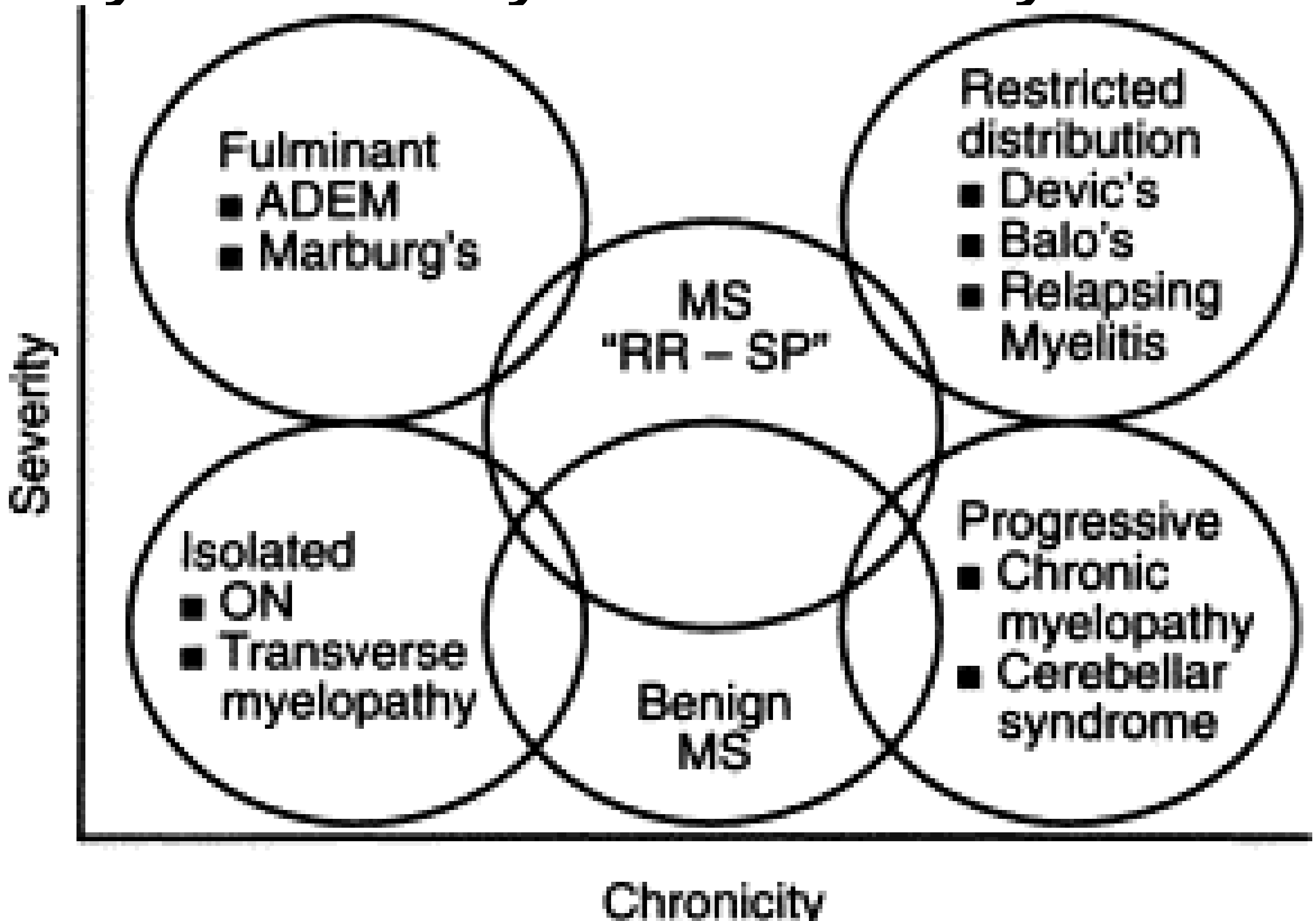
C

Balo's concentric sclerosis



Poser, Clin Neurol Neurosurg 106 (2004) 159-171

The spectrum of inflammatory demyelinating disorders of the CNS by chronicity and severity



Poser, Clin Neurol Neurosurg 106 (2004) 159-171

Tumefactive demyelination (TDL)

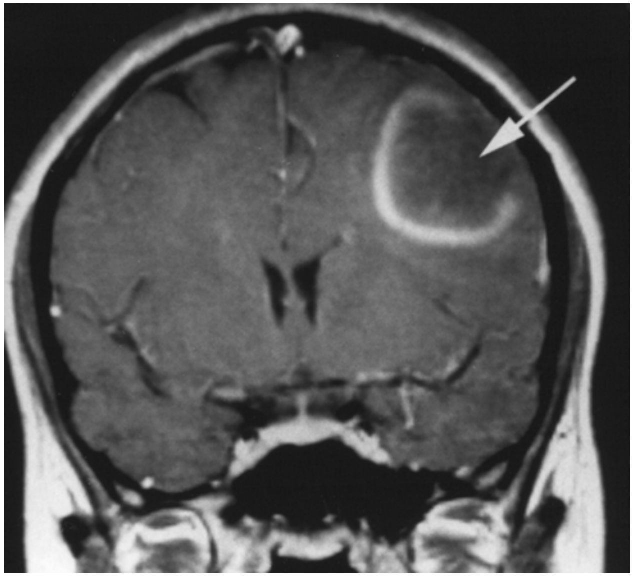
- Numerous clinical, pathological and radiographic reports, both MS and monophasic (CIS)
- N=31 bx proven TDL
- Clin: acute onset focal neurological deficit
  - age 10-77 (note older age), F>M
  - low risk of recurrence or definite MS (3 yrs)
- Path: identical to MS or ADEM
  - foamy macrophages
  - increased lipids
  - myelin loss with relative preservation of axons
  - reactive astrocytes
  - variable perivascular inflammation
  - sharp edged lesion vs. irregular margin (Poser 2004)
- Natural hx: often responsive to steroids

Kepes Ann Neurol 33 (1993) 18-27

Pathology – TDL vs. tumor

- TDL
  - Avascular
  - Foamy macrophages
  - Myelin loss, var. axon loss
  - Perivenular inflammation
  - Astrocytes
    - Occ. Mitotic figures
    - Occ. Pleomorphic
    - Reactive
  - Edema
  - Necrosis
  - Cystic change, cavitation
- Tumor
  - Hypervascular
  - Oligodendrocytes,
  - Small blue cells (lymphoma)
  - Axon loss
  - Astrocytes
    - Mitotic figures
    - Pleomorphic
    - Hyperchromatic nuclei
  - Edema
  - Necrosis
  - Cystic change, cavitation

Imaging – TDL



- N=21 biopsy-proven TDL
  - MS, CIS, ADEM, no data in 7
- Mean age 37 (10-58), F>M
- Solitary (8), multiple (13)
- Mean diameter 4.6cm (2-11cm)
- Frontal (8), frontoparietal (8), occipital (4), temporal (1)
- Enhancement (10), ring enhancement (9)
- Edema (8)
- Mass effect minimal (14), moderate (5), marked (2)
- Cystic change (4)
- Conclusions
  - CIS/TDL more enhancement than typical MS
  - Little mass effect or edema for lesion size

Dagher, Smirniotopoulos Neuroradiology 38 (1996) 560-565
Given, C. A. et al. Am. J. Roentgenol. 182 (2004) 195-199

Imaging – TDL vs. tumor

- TDL
  - “open-ring” (to gray matter)
  - little mass effect
  - little edema
  - supratentorial
  - decreased perfusion
  - shrink with steroids

  - corpus callosum involved
  - MRS hi CHO, low NAA
  - decreased MTR
- Tumor
  - closed or no ring
  - mass effect variable
  - edema variable
  - supratentorial or infratentorial
  - increased perfusion
  - steroid response (lymphoma)

  - corpus callosum involved
  - MRS hi CHO, low NAA
  - decreased MTR

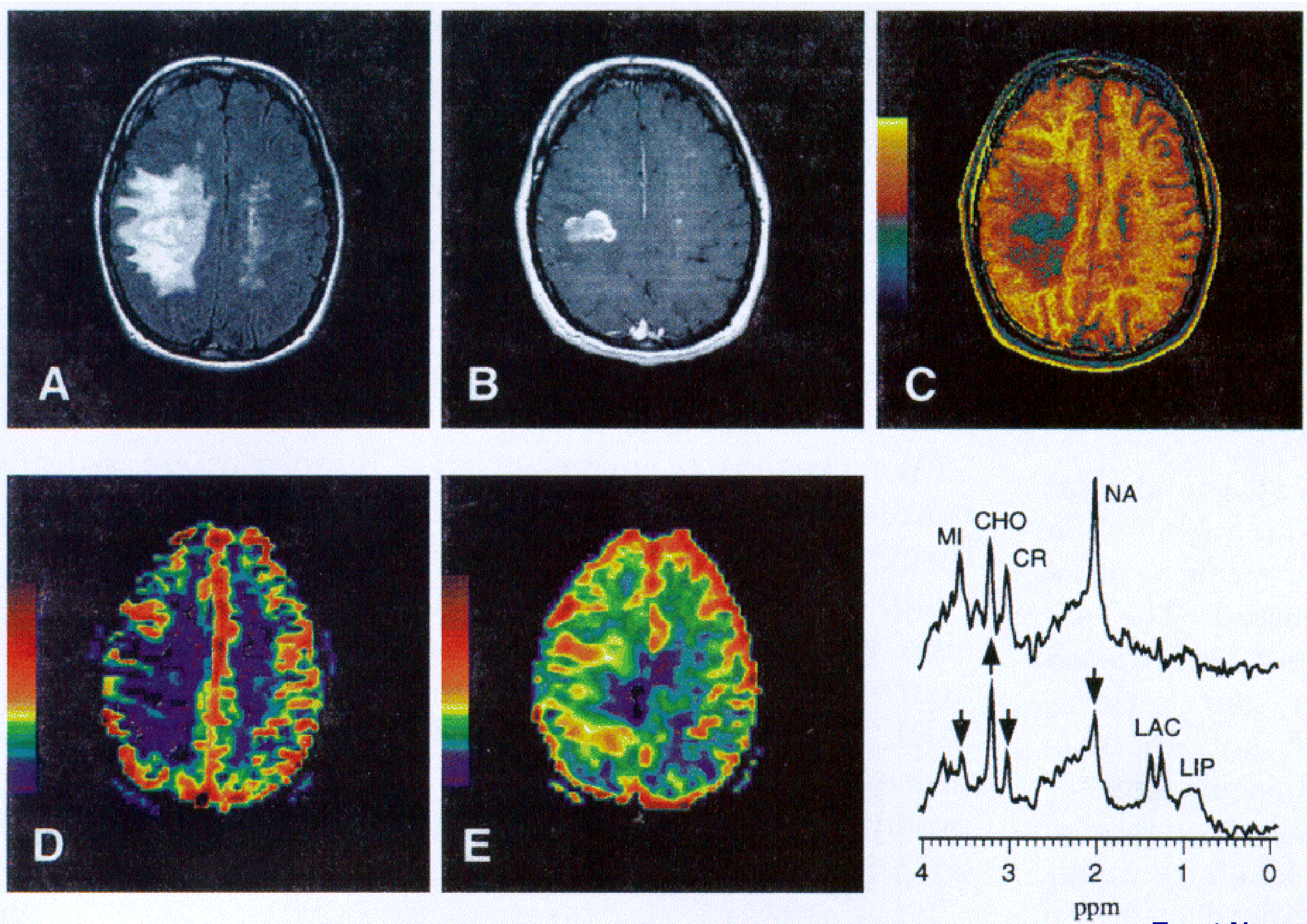
Brain biopsy –considerations

- Clinically isolated syndrome
- Solitary lesion
- Lesion size/mass effect
- Contrast enhancement
- Discordant symptoms
- Atypical location (not periventricular)
- Morbidity 3.5% mortality 0.7%

Physiologic MR imaging in MS

- MRI – T1 black holes (axon loss)
- MRI – post-gadolinium (acute BBB breakdown)
- Proton MR spectroscopy – metabolic entities
- Perfusion MRI – rCBF (vascularity)
- Magnetization transfer
- MR venography – perivascular pathology
- PET scan – metabolic state

Physiologic MR imaging in MS



(A) Fluid-attenuated inversion recovery image, (B) postgadolinium T1-weighted image, (C) magnetization transfer ratio map, (D) regional cerebral blood flow map, and (E) apparent diffusion coefficient map of an axial slice through the center of the large enhancing lesion in the right frontoparietal region. Localized ^{1}H spectra were obtained from a voxel (3.7 cc) in the lesion (bottom right, lower spectrum) and in the contralateral normal-appearing white matter (upper spectrum). Spectra are scaled (repeat time/echo time = 3,000/30 msec). See text for details. MI = myoinositol; CHO = choline; CR = creatine; NA = N-acetyl; LAC/LIP = lactate and lipids.

Ernst Neurology 51 (1998) 1486-1488

MR spectroscopy – metabolites

- Long echo time (TE 135 or 270ms)
  - CHO--choline: membrane turnover/density (e.g. myelin breakdown, inflammation, neoplasm)
  - NAA--*N*-acetylaspartate: neuron/axon/mitochon marker
  - lactate: anaerobic metabolism (e.g. inflammation)
  - creatine: cell metabolism
- Short echo time (TE 10-30ms)
  - lipids: myelin damage, lipoma, hi-grade glioma
  - myoinositol: glial cell marker
  - glutamate, glycine
- Use in MS: detect axon damage (incl. NAWM), correlates best with disability, serial scan/Rx

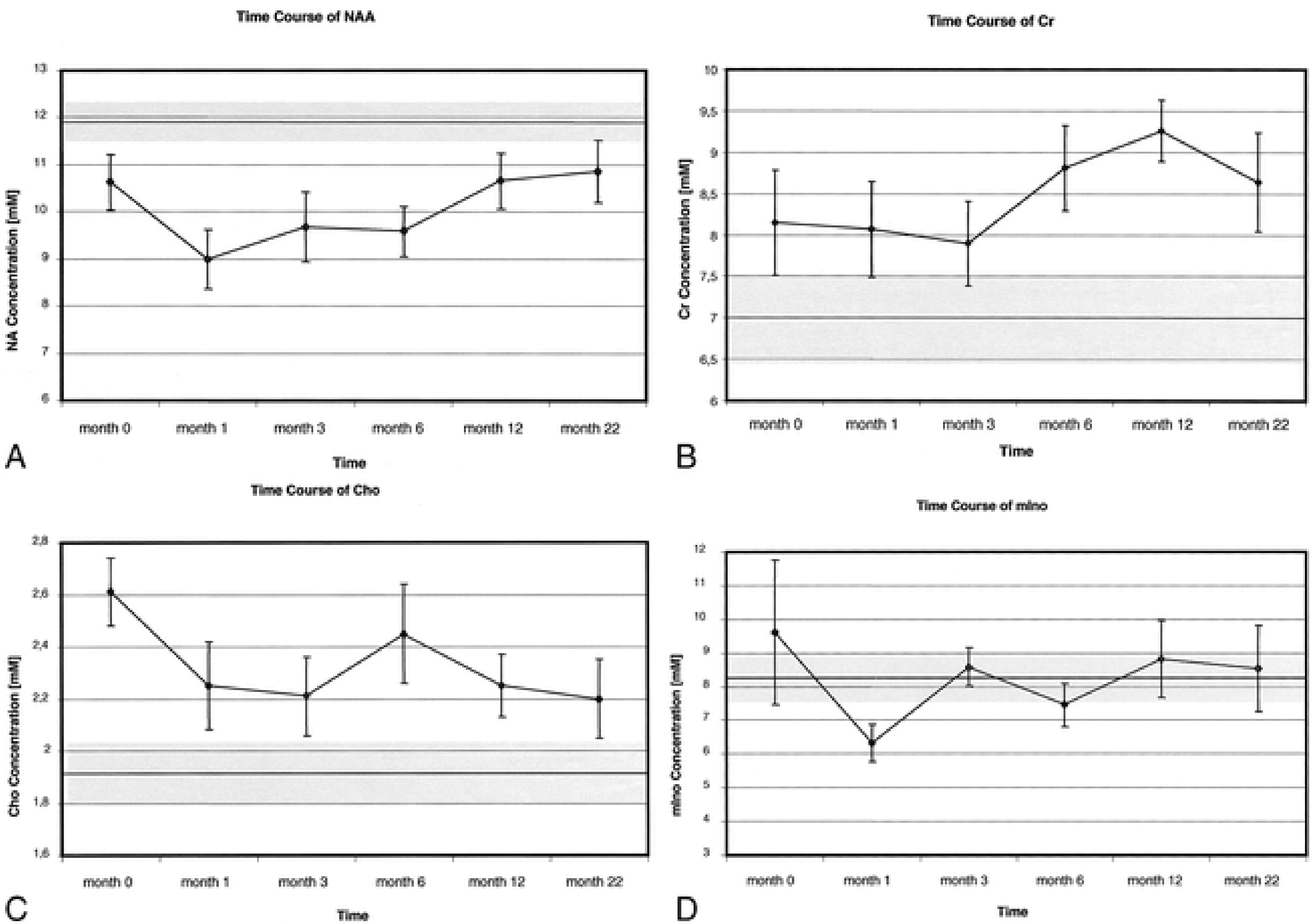
Bitsch AJNR 20 (1999) 1619-1627

proton MR spectroscopy

	acute demyelinization	chronic demyelinization	low grade glial tumor	high grade glial tumor	lymphoma
Cho	↑(R)	Normal or ↑	↑	↑	↓
NAA	↓ (R)	↓↓	↓	↓↓	↑
Lac	↑↓ (R)	↓	↑↓	↑↓	
Cr		Normal			
Lipid	↑↓ (R)	Normal	↑↓		

(R) – reversibility with serial scans

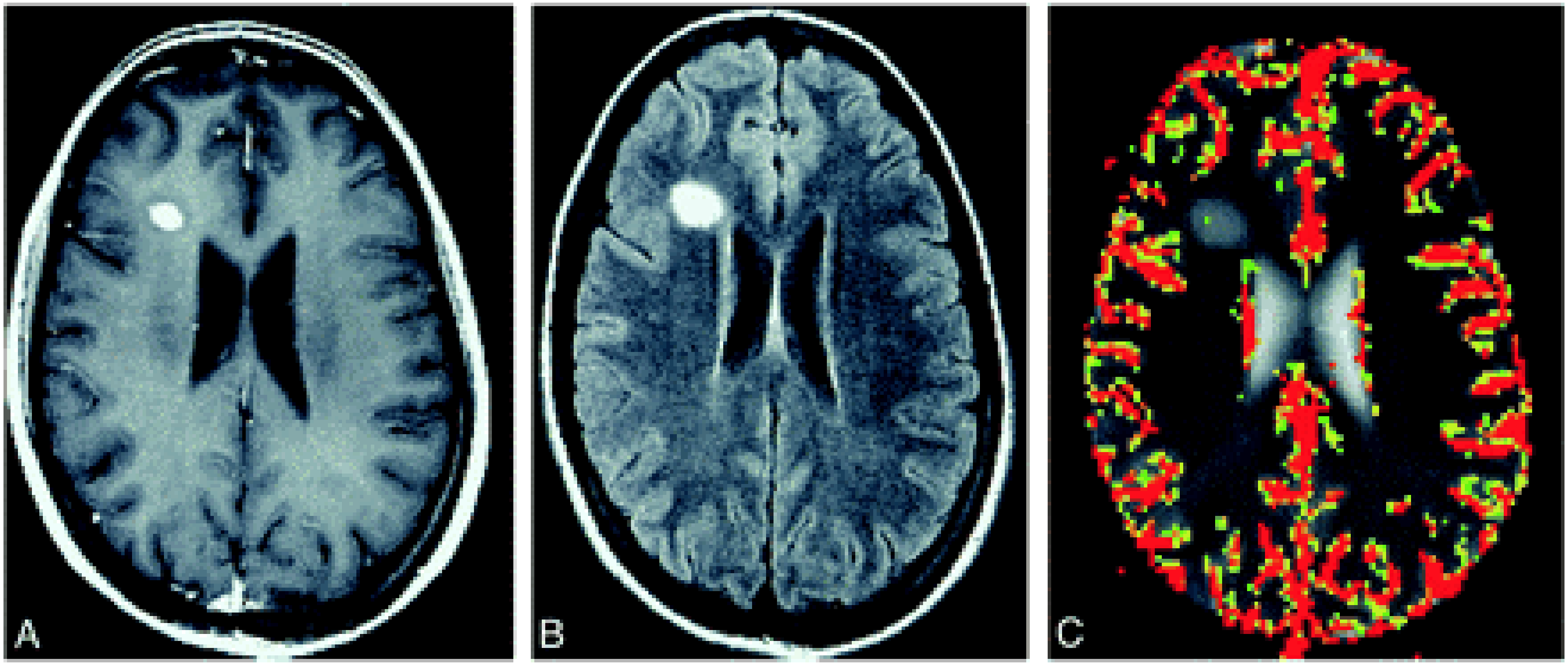
Serial MR spectroscopy - MS



The absolute concentrations of the metabolites as a function of time. The mean of the healthy control subjects ± 1 SEM is indicated by the *horizontal bars.*
A, Time course of NAA. After a reduction in month 1, a slow recovery is visible until month 22.
B, Time course of Cr. There is a significant elevation from month 3 to months 6 and 12.
C, Time course of Cho. Note the significant decrease from month 0 to month 3.
D, Time course of *myo*-inositol. No systematic changes are recognizable.

Mader, et al AJNR 21 (2000) 1220-1227

Dynamic contrast-enhanced T2



TDL in a 22-year-old woman.

A, Contrast-enhanced T1-weighted image (600/14/1) shows a well-circumscribed solidly enhancing mass in the right frontal lobe.

B, Fluid-attenuated inversion recovery image (9000/110/1) shows a mild degree of signal abnormality around the lesion.

C, Color overlay of rCBV map shows no evidence of increased blood volume

Cha, et al AJNR 22 (2001) 1109-1116

Relative cerebral blood volume

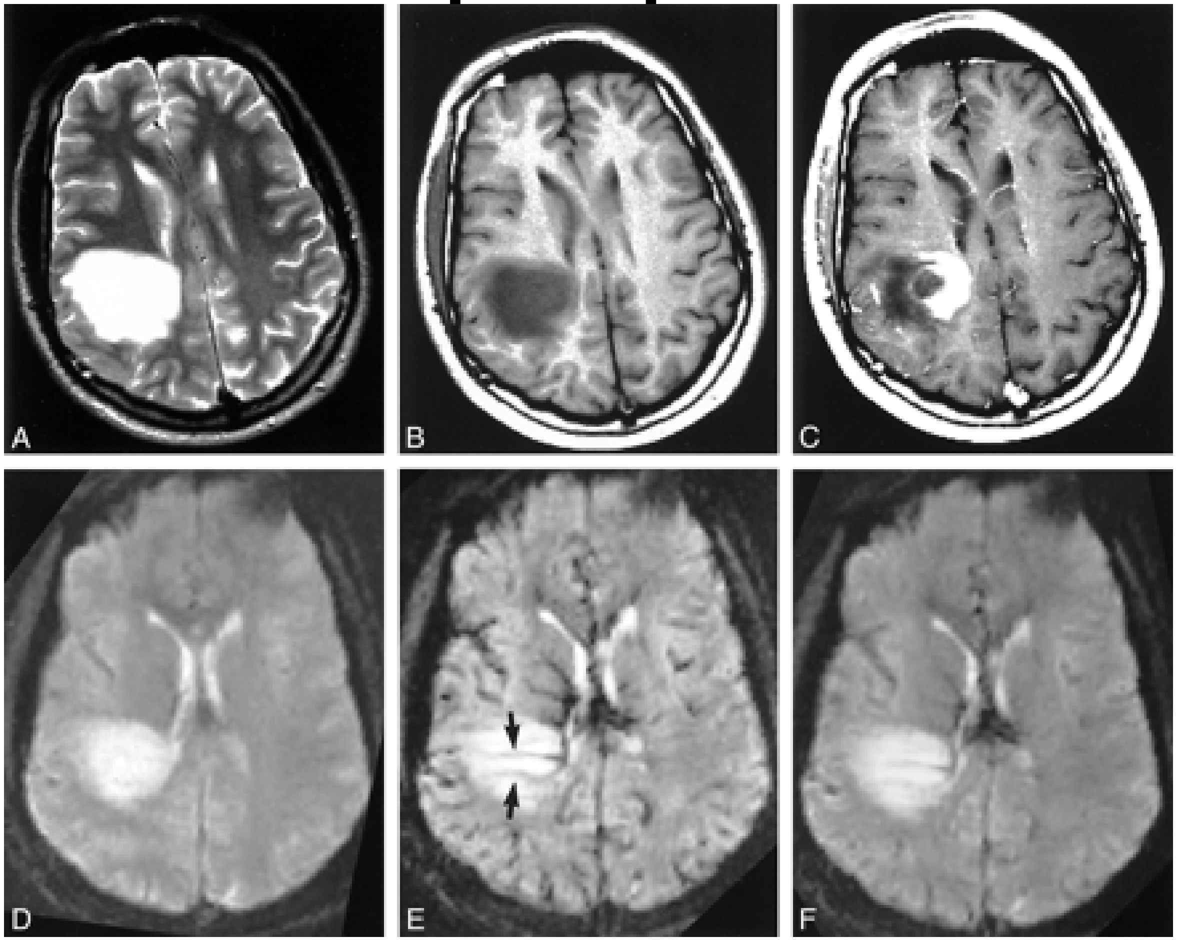
	Range of rCBV	Mean rCBV*	SD
Tumefactive demyelinating lesion (n = 12)	0.22–1.79	0.88	0.46
Intracranial neoplasms (n = 11)	1.55–19.2	6.47	6.52

* P = .009

Patient No.	Age (y)	Sex	Pathologic Diagnosis	Maximum Tumor rCBV
1	39	F	Anaplastic mixed glioma	19.2
2	63	F	Glioblastoma	18.7
3	51	M	Anaplastic astrocytoma	8.7
4	70	M	Glioblastoma	5.8
5	70	M	Glioblastoma	3.23
6	28	F	Oligodendroglioma	2.27
7	29	F	Anaplastic astrocytoma	4.87
8	54	M	Primary cerebral lymphoma	2.14
9	51	M	Primary cerebral lymphoma	1.55
10	51	M	Primary cerebral lymphoma	2.82
11	37	M	Primary cerebral lymphoma	1.94

Cha, et al AJNR 22 (2001) 1109-1116

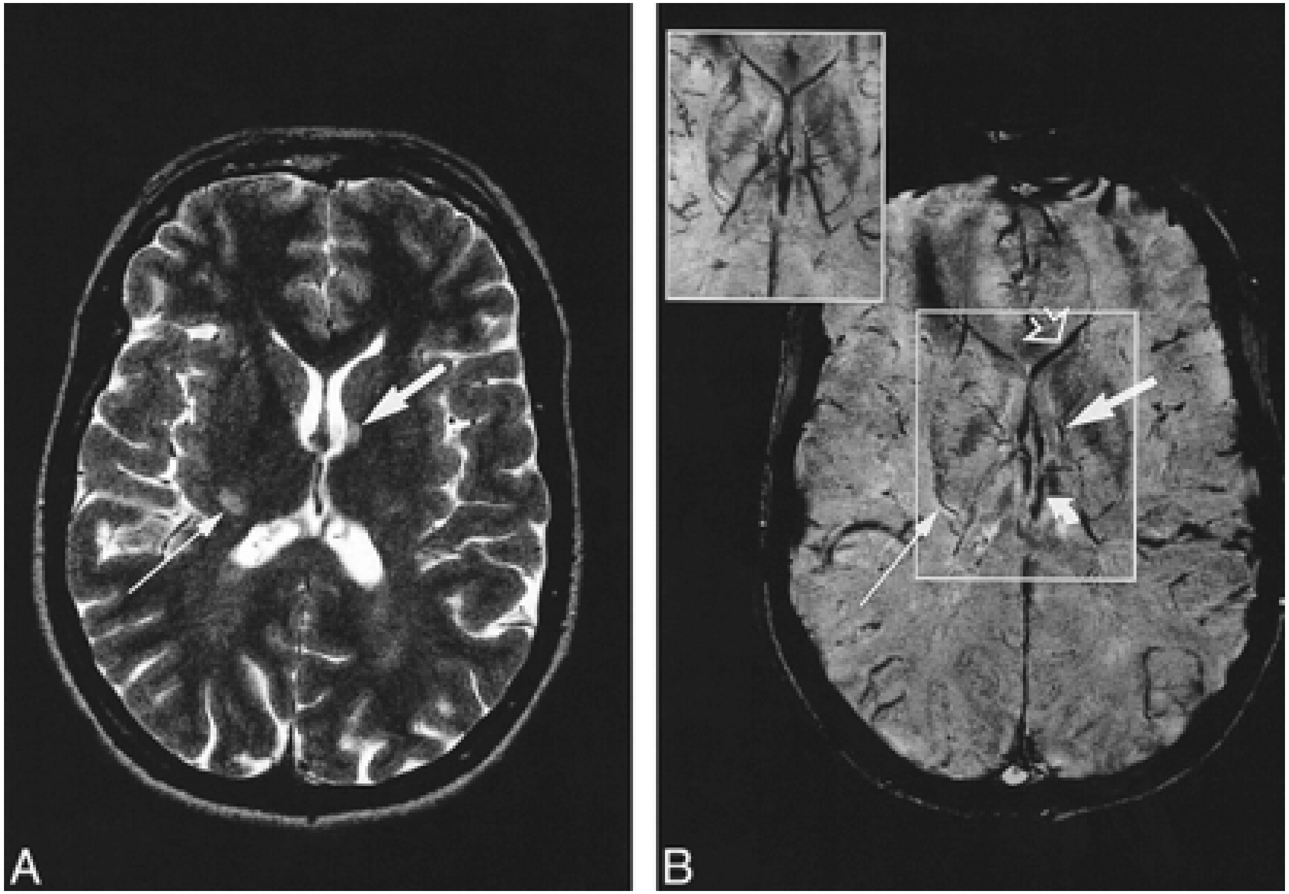
Perivenular plaque distribution



E, Dynamic T2*-weighted image (1000/54/1) obtained during IV administration of contrast agent shows several periventricular, linear vessel-like structures (*arrows*) running through the center of the lesion near a dilated subependymal vein. The dominant lesion itself shows no signal loss.

Cha, et al AJNR 22 (2001) 1109-1116

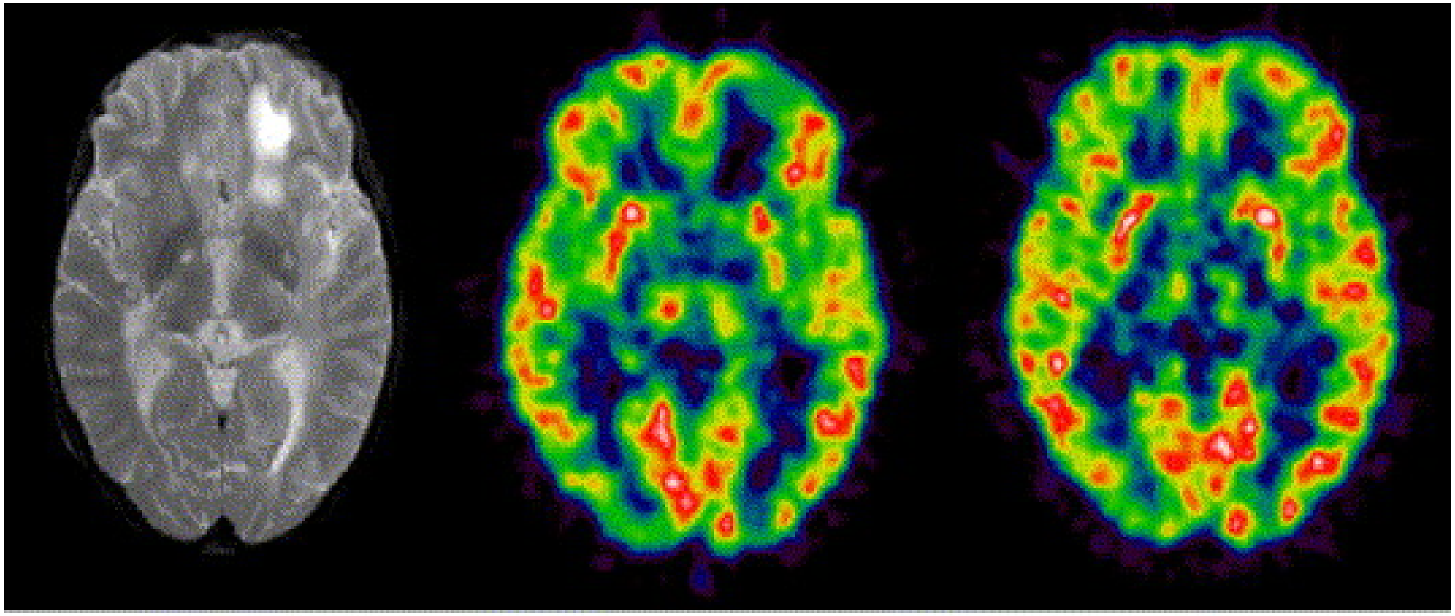
MR venography



A and *B,* Axial T2-weighted MR image (7000/112/2) (*A*) at the level of the lateral ventricles and corresponding contrast-enhanced MR venogram (67/50/1) (*B*). The *inset* in *B* is the minimum intensity projection image calculated over 7.5 mm of the *boxed area.* The form and orientation of the left periventricular MS lesion (*wide arrow*) corresponds to the course of the longitudinal caudate vein. The lesion at the posterior limb of the right internal capsule (*thin arrow*) corresponds to the course of a striate vein. *Curved arrow* indicates internal cerebral vein; *open arrow,* septal vein

Tan et al, AJNR 21 (2000) 1039-1042

PET scanning



MRI (Acute) PET (CMRglc) Acute PET (CMRglc) After 20 days

MRI and PET of a patient admitted with an acute large plaque in the left orbitofrontal region. The PET scan was repeated after 20 days. The MRI scan was unchanged but the PET scan showed an increase in the glucose metabolism, both in the frontal white matter and in the frontal cortex on the left side.

Sorensen, et al. J Neurol Sci 245 (2006) 99-102

Conclusions

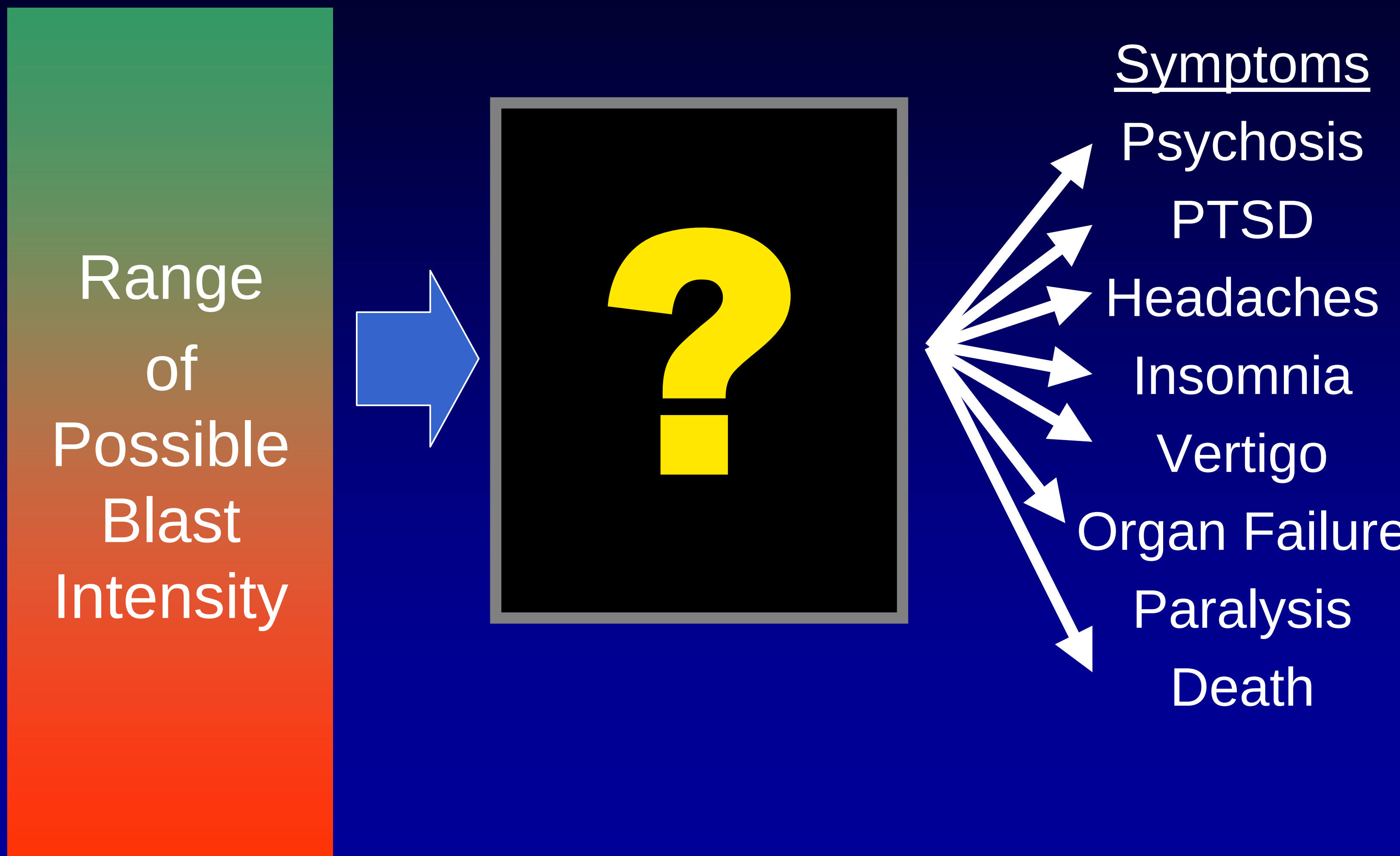
- This appears to be the second reported case of relapsing-remitting tumefactive MS
- Consider TDL in differential dx of cerebral mass lesions
- Some radiographic features suggestive
  - "open-ring" enhancement, little mass effect, little edema
- Most CIS/TDL pts do not later develop CDMS
- Most CIS/TDL pts who do have MS develop more typical (<2cm) lesions
- Optimal therapy for tumefactive MS unknown, though proper diagnosis may prevent injurious therapy
- Diagnostic options – MRS, PET, rCBV, MTR have ***NOT*** replaced brain biopsy as definitive diagnostic entities

Big Trend

- U.S. troops increasingly face chaotic urban warfare
- Impact of Improvised Explosive Devices (IEDs) increasing
- Identified as No.3 current goal for the Pentagon
- 88% of E2 treatments due to IED or mortars


www.globalsecurity.org

Major Challenge

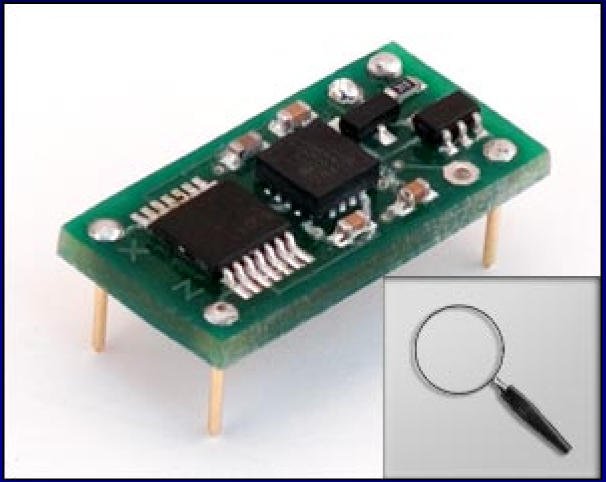


Three Year Projection

- Develop **SAIBR**: <u>S</u>oldier <u>A</u>rmor <u>I</u>ntegrated <u>B</u>last <u>R</u>ecorder
- Pressure and accelerometry sensing + datalogging
- Compact, low-profile, field maintainable
- Essentially a “blast dosimeter”

Approach for 3 Year Target

- Phase 0: Define specs
- Phase 1: Prototype using commercially available components
- Phase 2: Design and build integrated system
- Testing, testing, testing



www.dimensionengineering.com

5 Year View

- Phase 3: Production ramp-up and widespread deployment
- Need manufacturing partners (e.g., makers of helmets or armor)
- Integration with military electronic health records

Rationale for 5 Year View

- SAIBR will be most powerful once extensively deployed.
- Data mining for threshold effects, efficient triage, blast injury mechanisms
- Immediate blast dosimetry could enable “golden hour” drug interventions.

Closing

- World stockpiles of Semtex (plastic explosive) may be 40 kilotons.
- Estimates of looted munitions in Iraq are as high as 250 kilotons.
- There is a lot of work ahead of us!

Imaging genetic effects in schizophrenia

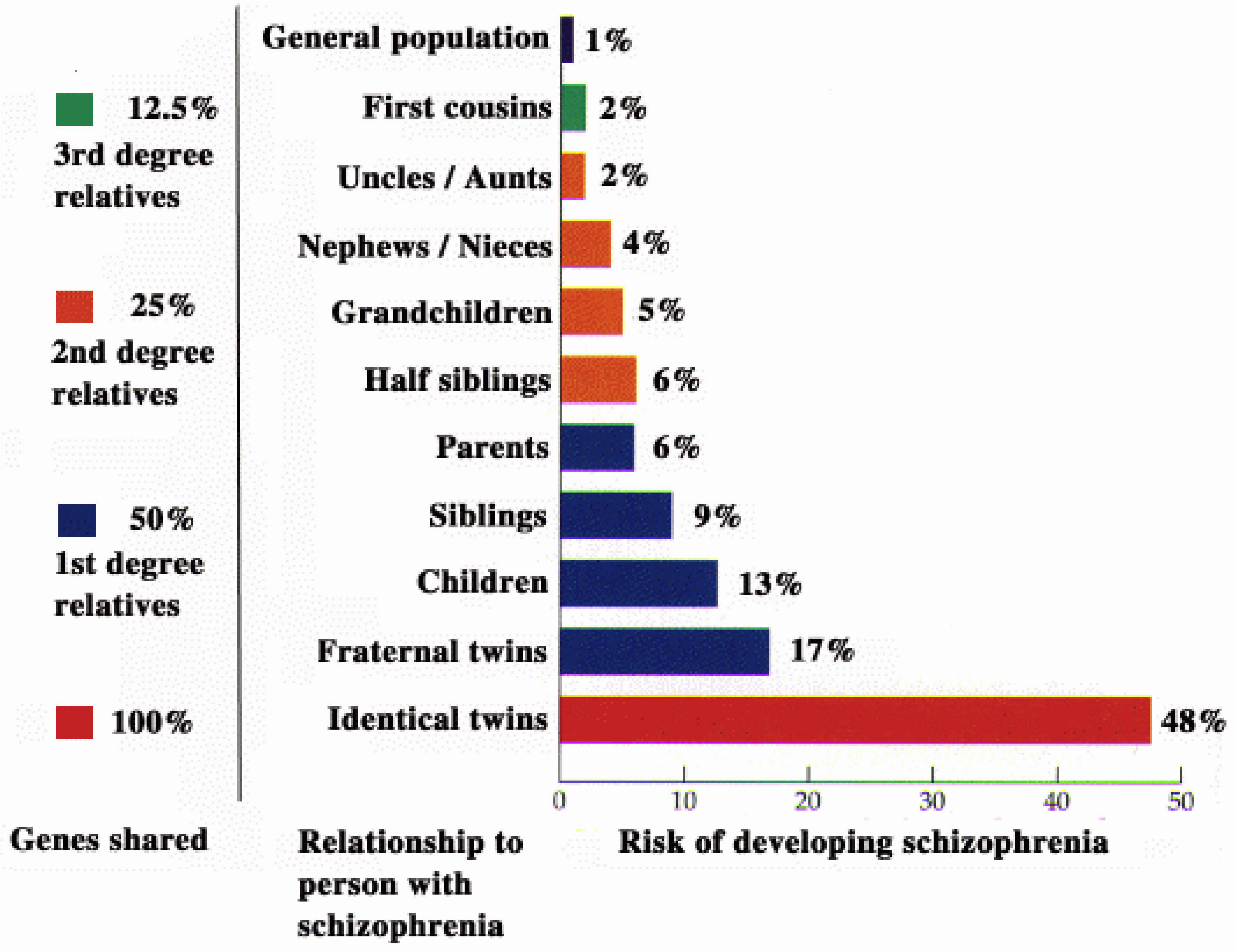
Stephen Lawrie
Sackler Senior Clinical Research Fellow
Professor of Psychiatry & Neuro-Imaging
University of Edinburgh

sMRI systematic reviews in schizophrenia

- reduced whole brain volume (by ~3% Ward, Schiz Res 1996;197-213)
- corpus callosum similarly (Woodruff, JNNP 1995; 58: 457-61)
- reduced hippocampal and amygdala volume (by about 4% each: Nelson, Arch Gen Psych 1998; 55: 433-40)
- reduced pre-frontal & medial temporal lobe (MTL) volumes (Lawrie & Abukmeil, Br J Psych 1998;172: 110-120)
- reduced superior temporal gyrus (STG) & increased globus pallidus volumes (Wright, Am J Psych 2000; 157: 16-25)
- reduced thalamus (Konick & Friedman, Biol Psych 2001; 49: 28-38)

- Also, 15 VBM studies consistently find reduced GM in MTL and STG (Honea et al, Am J Psych 2005; 162: 2233-45)

Schizophrenia Risks



© Gottesman, 2004

sMRI ROI studies of relatives

- Relatives have smaller MTLs than controls
  (Keshavan 1997 & 2002; Lawrie 1999 & 2001; Schreiber 1999; Seidman 1997 & 1999 – but see McDonald 2002 & 2006)

- Schizophrenics have smaller MTLs than relatives
  (Lawrie 1999 & 2001;O'Driscoll 2001;Steel 2002 – but see Staal 2000, McDonald 2006)

- Best evidence is for hippocampal differences
  (Waldo 1994;Harris 2002;Seidman 2002;van Erp 2002 – but see Schulze 2003).

- …and is supported by twin studies
  (Suddath 1990; Baare 2001; Narr 2002; van Erp 2004)

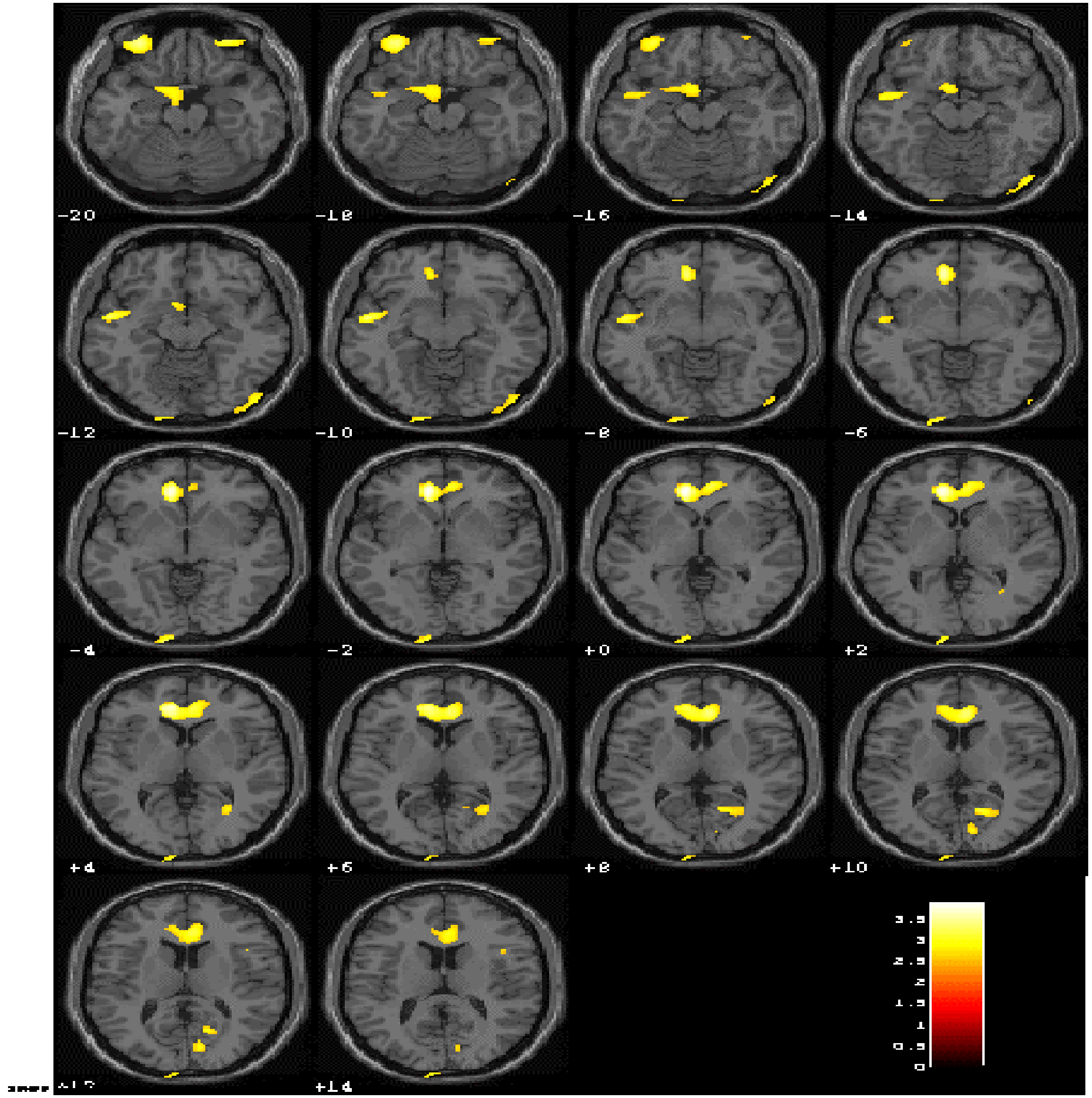
- …and g-e risk factor studies
  (DeLisi 1988; Stefanis 1999; McNeil 2000; Cannon 2002)

NB Boos et al meta-analysis (Archives 2007) of relatives finds hippocampal reductions in relatives Vs controls (ES 0.3) and additional differences between relatives and patients (ES 0.5)

VBM at T1 in EHRS:

GM deficits in HR cf Controls

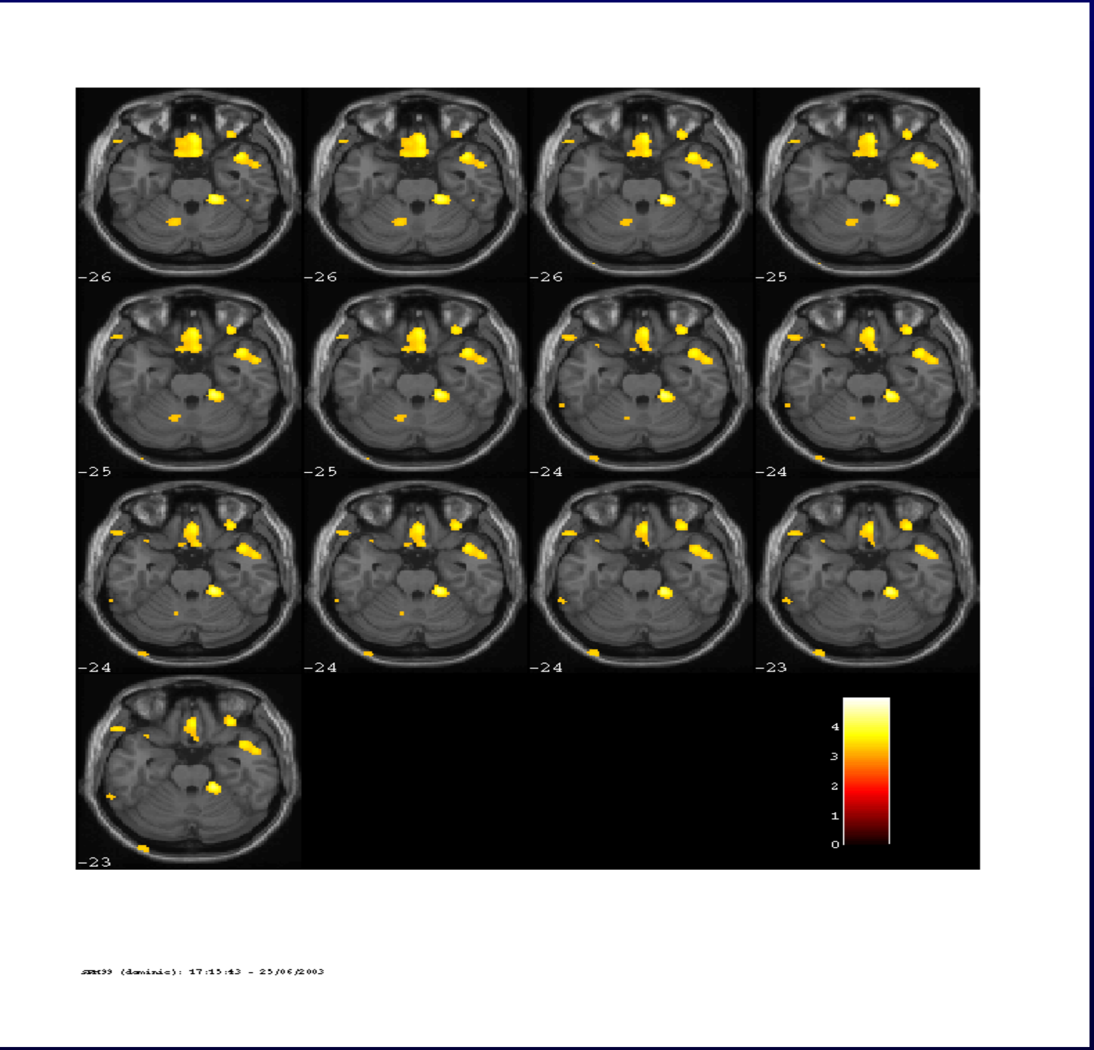
(Job et al, Schizo Res 2003)



GM REDUCTIONS IN HIGH RISK SUBJECTS PREDICTS SCHIZOPHRENIA

Greater reductions in GM density between first two sMRI scans in 8 high risk subjects with psychotic symptoms who went on to develop schizophrenia, an average of 2.5 years later, controlling for changes in 10 high risk subjects with psychotic symptoms who did not develop schizophrenia

(Job et al 2005 Neuroimage)



A receiver operator characteristic (ROC) curve analysis of GM change in temporal lobes showed that these were more strongly predictive of schizophrenia than the strongest behavioural and cognitive predictors (Job et al 2006 BMC Medicine).

Functional imaging consistently identifies ‘hypofrontality’ but it depends….

<u>‘Hypo-’ and ‘Hyper-’ frontality</u>

- 21 resting PET studies ES –0.64 (95%CI –0.91 to –0.38) & 9 activated studies overall ES –1.13 (–1.53 to –0.73)

  (Zakzanis & Heinrichs, JINS 1999; 5: 556-66; see also Davidson & Heinrichs Psych Res 2003 122: 69-87 and Hill et al Acta Psychiatr Scand. 2004 110:243-56.)
- Glahn et al (*Hum Brain Mapp 2005 25: 60-9) reviewed 12 N-back studies to find DLPFC ‘hypofrontality’ and ‘hyper-frontality’ in Ant. Cing. & (L) frontal pole

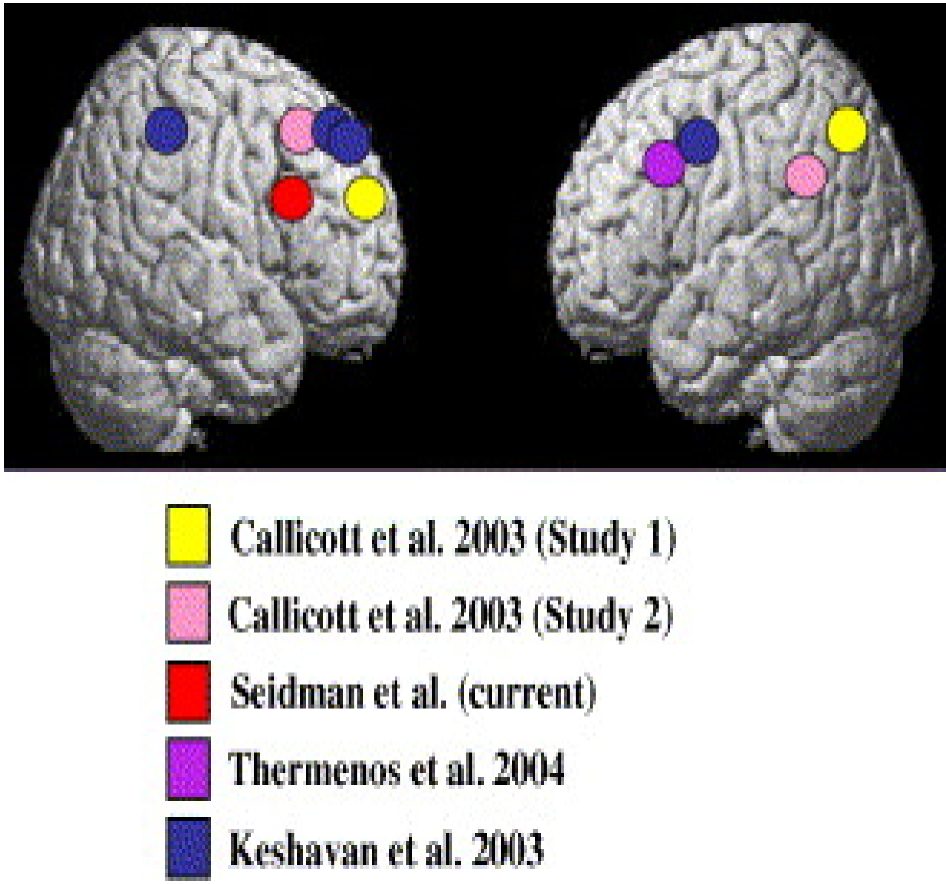
<u>‘Hyper-’ and ‘Hypo-’ temporality</u>

- 13 SPECT studies show effect sizes from 0.25 (superior) to 2.0 (inferior); 6 PET studies show effect sizes from 0.14 (right) to 1.3 (superior) (Zakzanis, Psychol Med 2000; 30: 491-504)
- Achim & Lepage (*Br J Psych 2005 187: 500-9) examined 18 episodic memory studies and found consistent (L) IPFC and (Bi) MTL reductions in activation

Functional imaging replications in relatives - SPECT, PET and fMRI studies

‘Hypo-’ & compensatory ‘Hyper-’ frontality

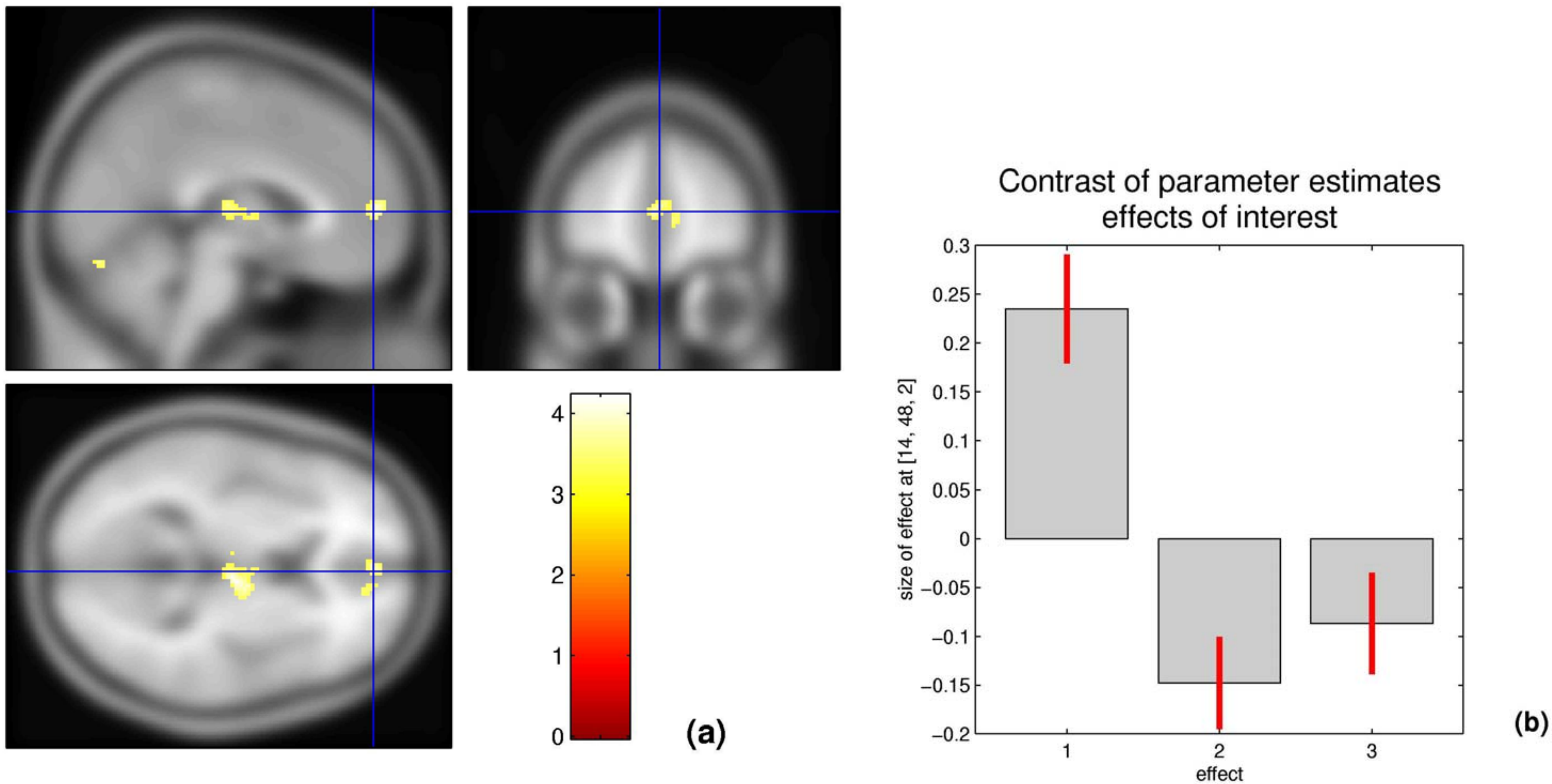
- Berman (1992) – only Sch twins hypofrontal on WCST
- Blackwood (1999) – 36 relatives reduced in (L) IPFC and AC at rest
- O’Driscoll (1999) – NS perfusion diffs in 17 relatives
- Spence (2000) – NS perfusion diffs in 10 ‘obligates’
- Keshavan (2002) – reduced BOLD in DLPFC & IPC on MGS task
- Callicott (2003) – (R)DLPFC increased BOLD on matched N-back task
- Thermenos (2004) – increased BOLD in (L) DLPFC, AC, thalamus & PHG on CPT
- Whalley (2004) – increased parietal & reduced front-thalamo-cerebellar BOLD on HSCT (etc)
- Seidman (2005) - exaggerated fMRI response in DLPFC on auditory WM



Disconnectivity

Replicated reduced fronto-frontal connectivity in relatives compared to controls on SPET (Spence et al, 2000) and fMRI (Whalley et al 2005)

fMRI under-activation differences in all high risk subjects versus healthy controls (total n = 100)



Hayling task:
Parametric analysis: increased activation with increasing task difficulty

Whalley et al 2004 Brain 127:478

Genetic risk factors for schizophrenia

Gene/locus	**Chromosomal location**	**Evidence in schizophrenia**	**Evidence in bipolar disorder**
Dysbindin	6p22	+ + + + +	
Neuregulin 1	8p12	+ + + +	+
DISC 1	1q42	+ + +	+
RGS4	1q23	+ +	
COMT	22q11	+	+
DAOA (G72)/G30	13q33	+ +	+ +
BDNF	11p13		+ +
DAO	12q23	+ +	

Craddock et al, Journal of Medical Genetics 2005;**42**:193-204

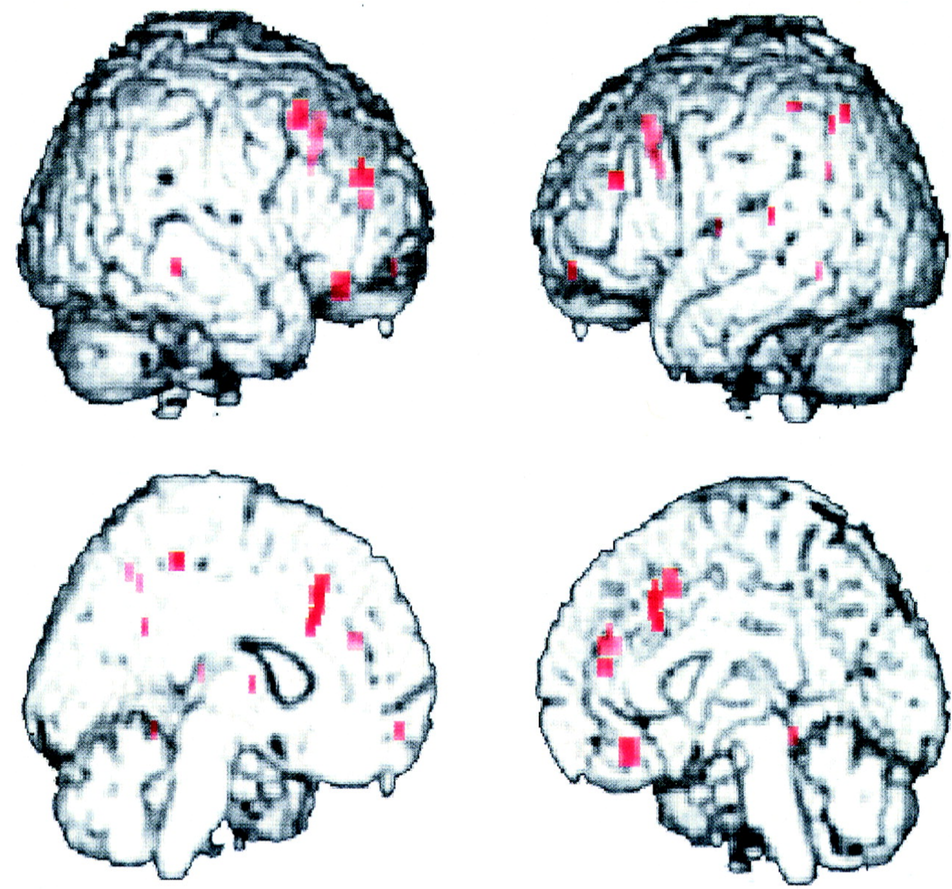
Genetic imaging in the EHRS and in schizophrenia

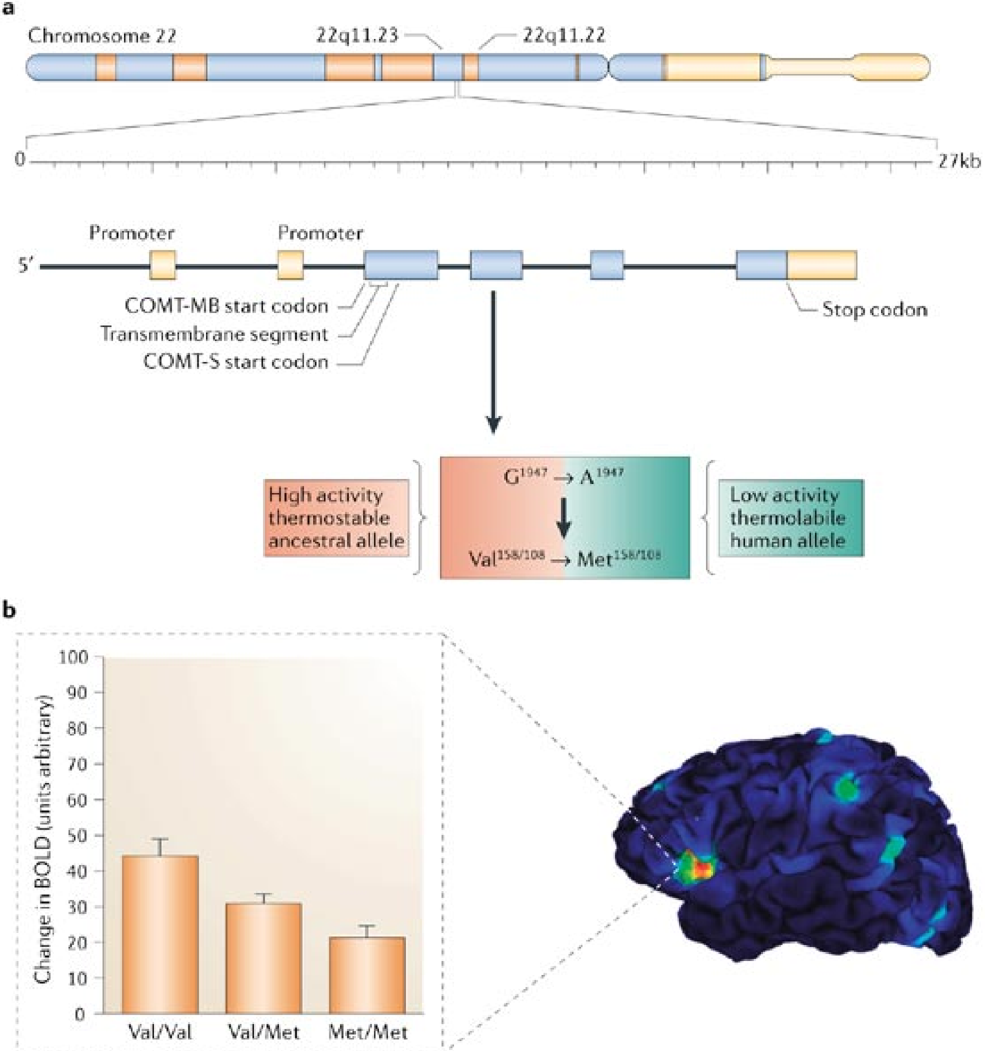
Genetic imaging at NIMH

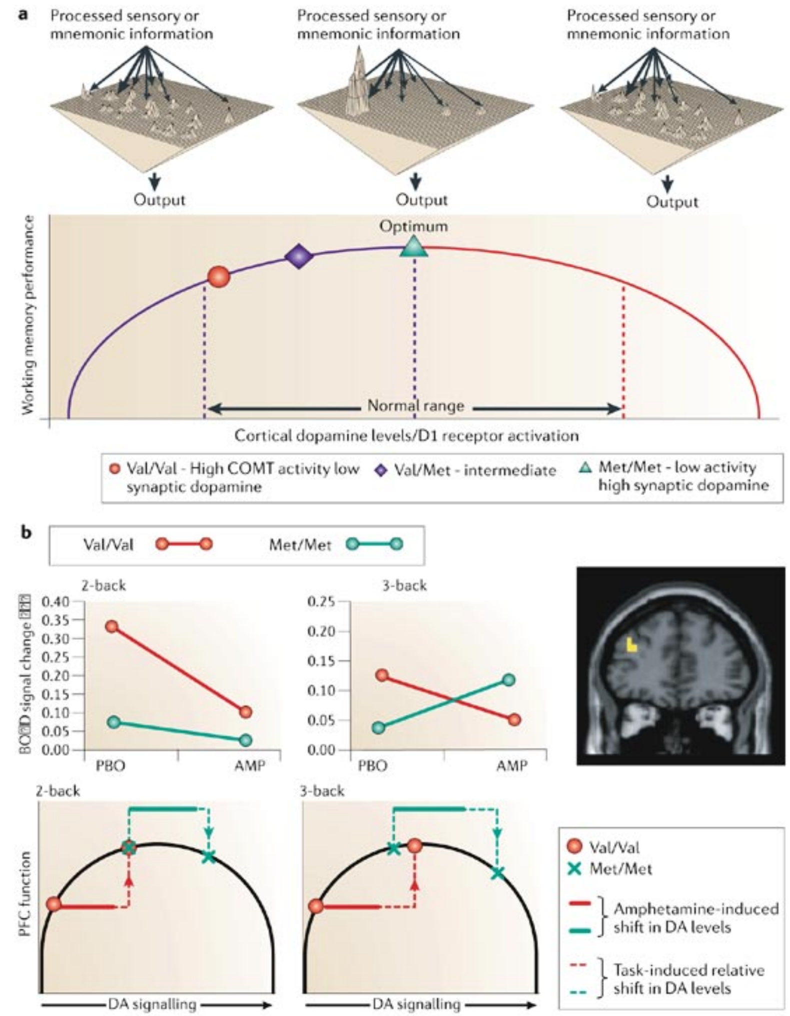
- Egan et al (2001)
  Effect of COMT Val 108/158 Met genotype on frontal lobe function and risk for schizophrenia.

  Proc Natl Acad Sci U S A. 2001 Jun 5;98(12):6917-22.
  Epub 2001 May 29.

  Val/Val individuals showed a greater fMRI response (and by inference, greater inefficiency, as performance is similar) than Val/Met individuals who have greater activation than Met/Met individuals in DLPFC and AC.



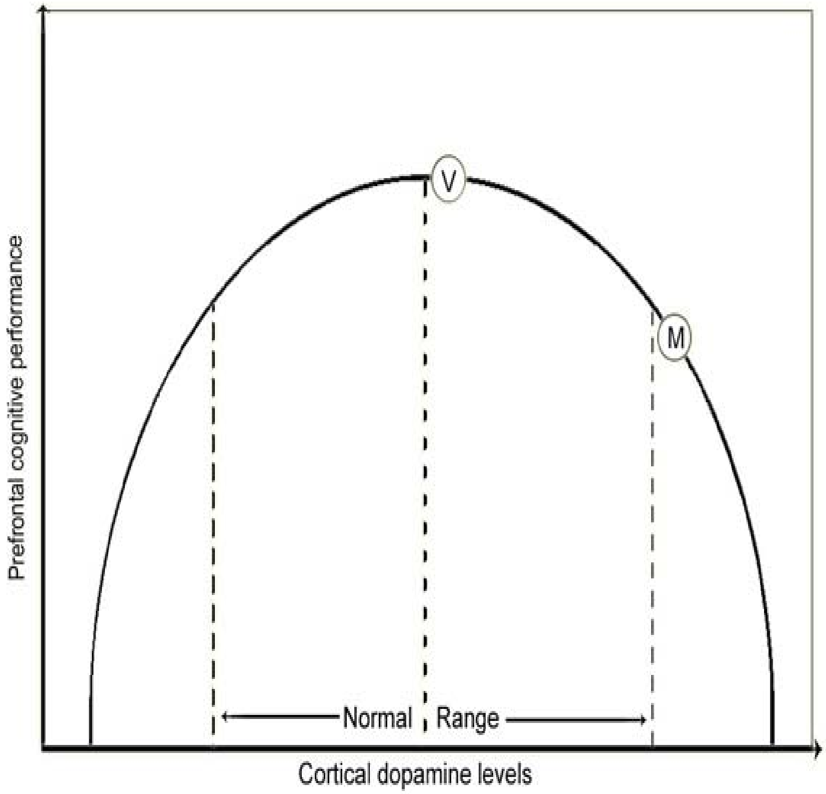


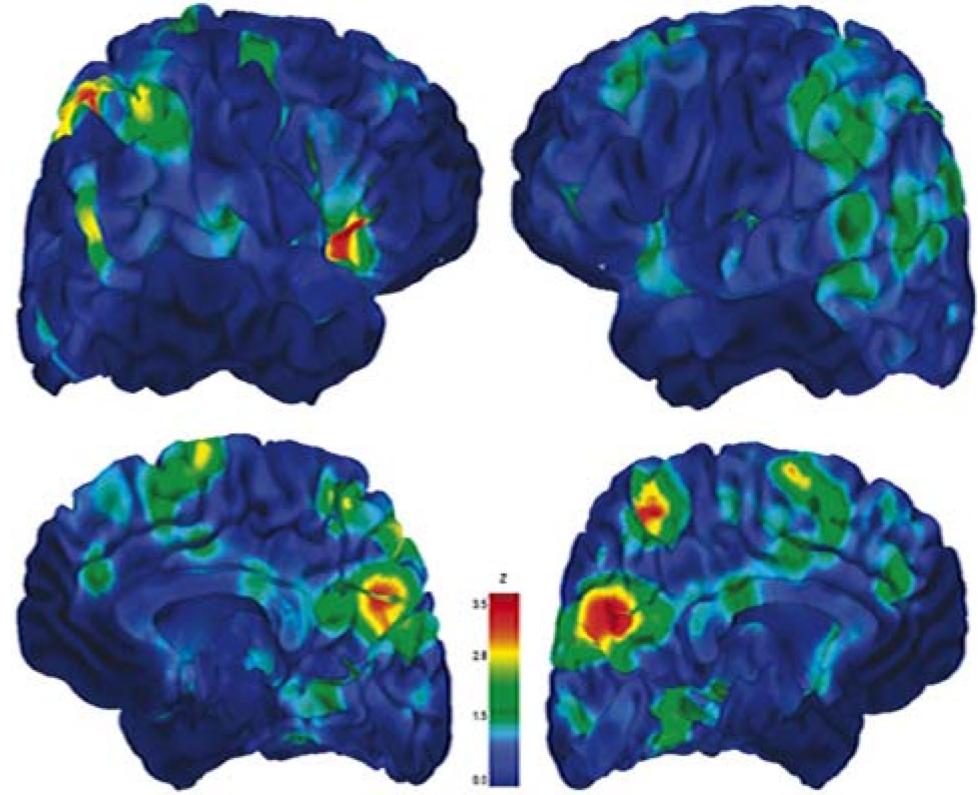


Meyer-Lindenberg and Weinberger *Nature Reviews Neuroscience* **7**, 818–827 (October 2006)

Intermediate phenotypes and genetic mechanisms of psychiatric disorders

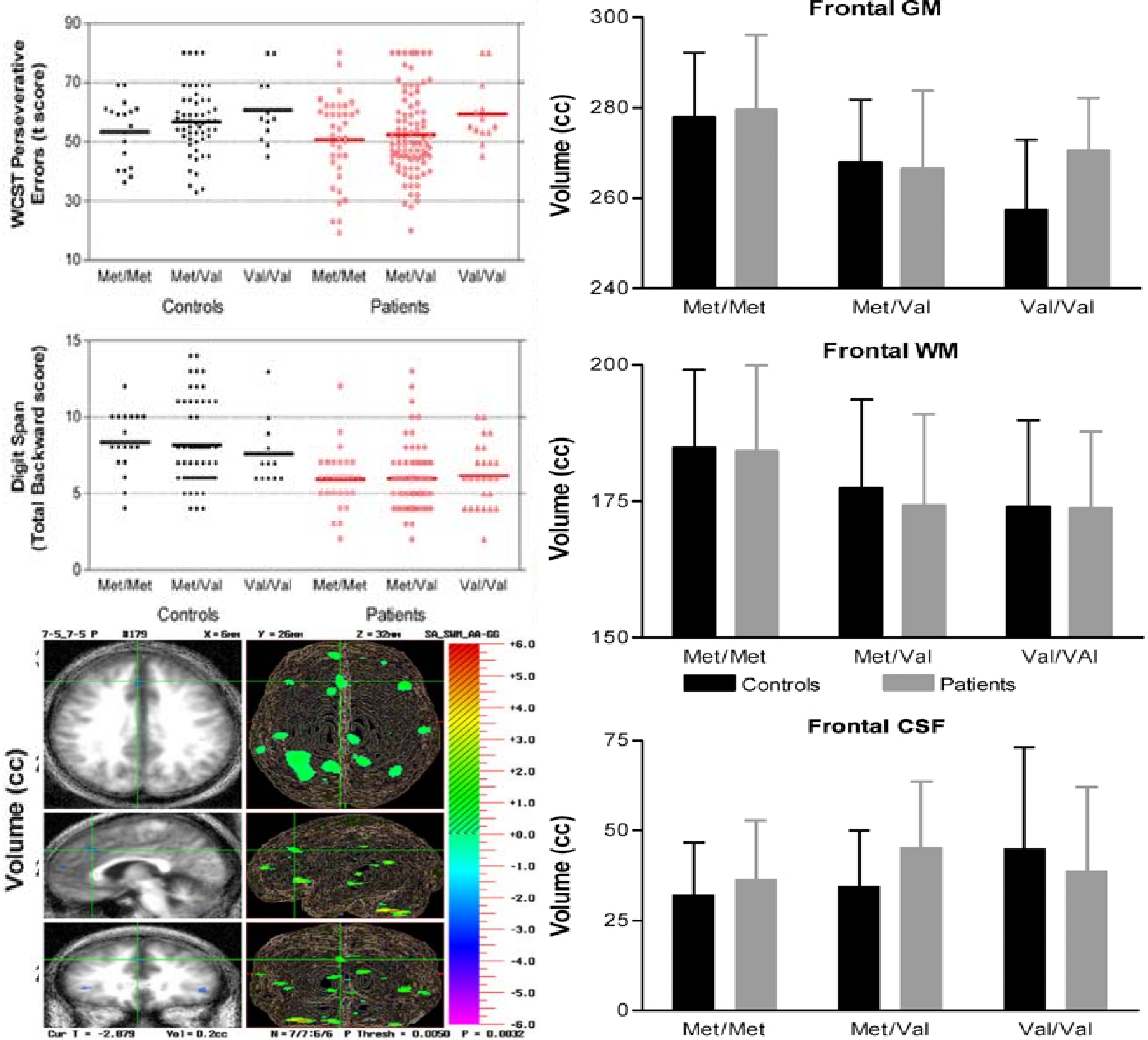
nature REVIEWS NEUROSCIENCE





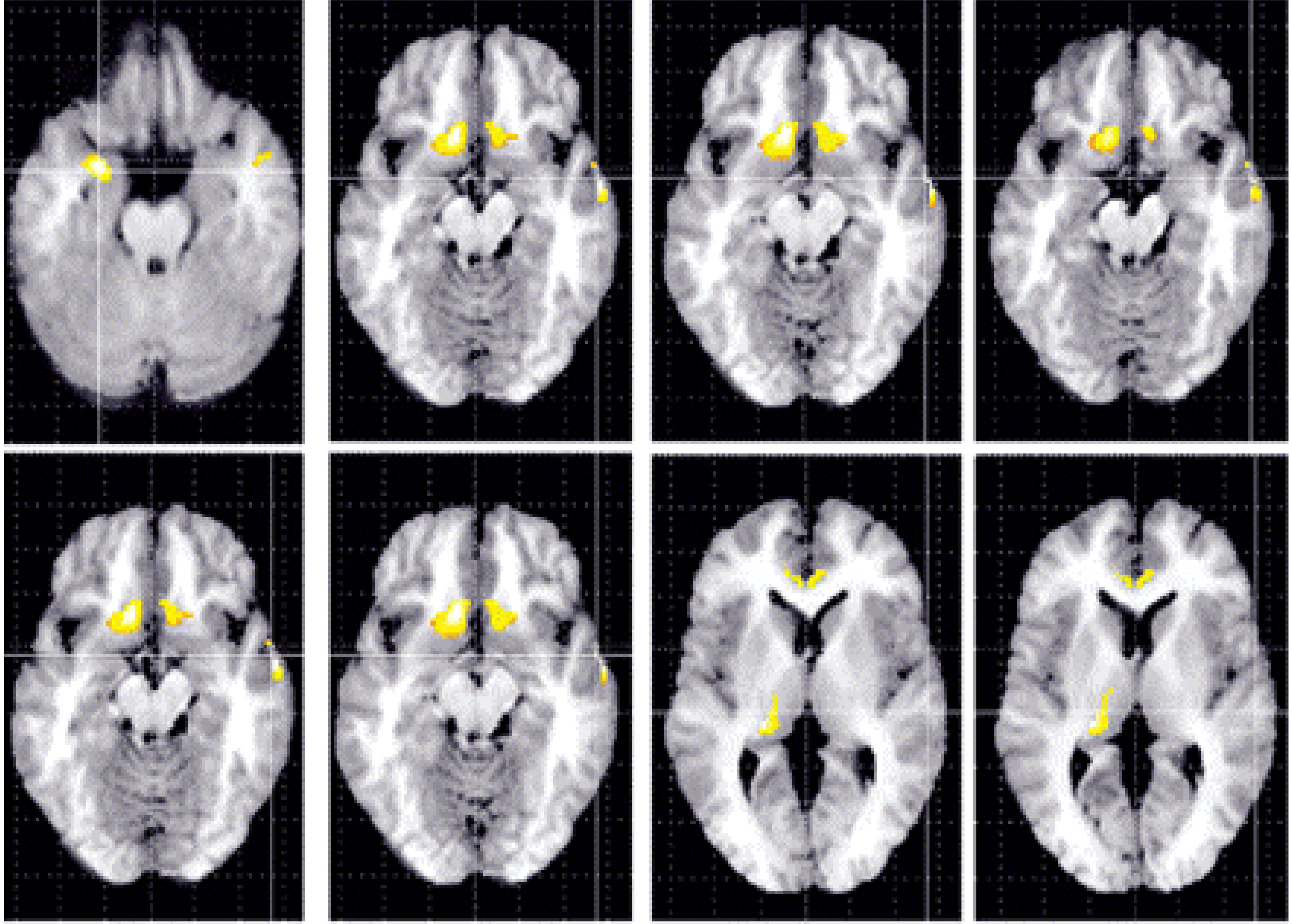
COMT haplotype variation affects human prefrontal function
A Meyer-Lindenberg
Molecular Psychiatry (2006) **11,** 797.

MM < VV on one-back



Catechol-*O*-methyl transferase Val158Met gene polymorphism in schizophrenia: working memory, frontal lobe MRI morphology and frontal cerebral blood flow

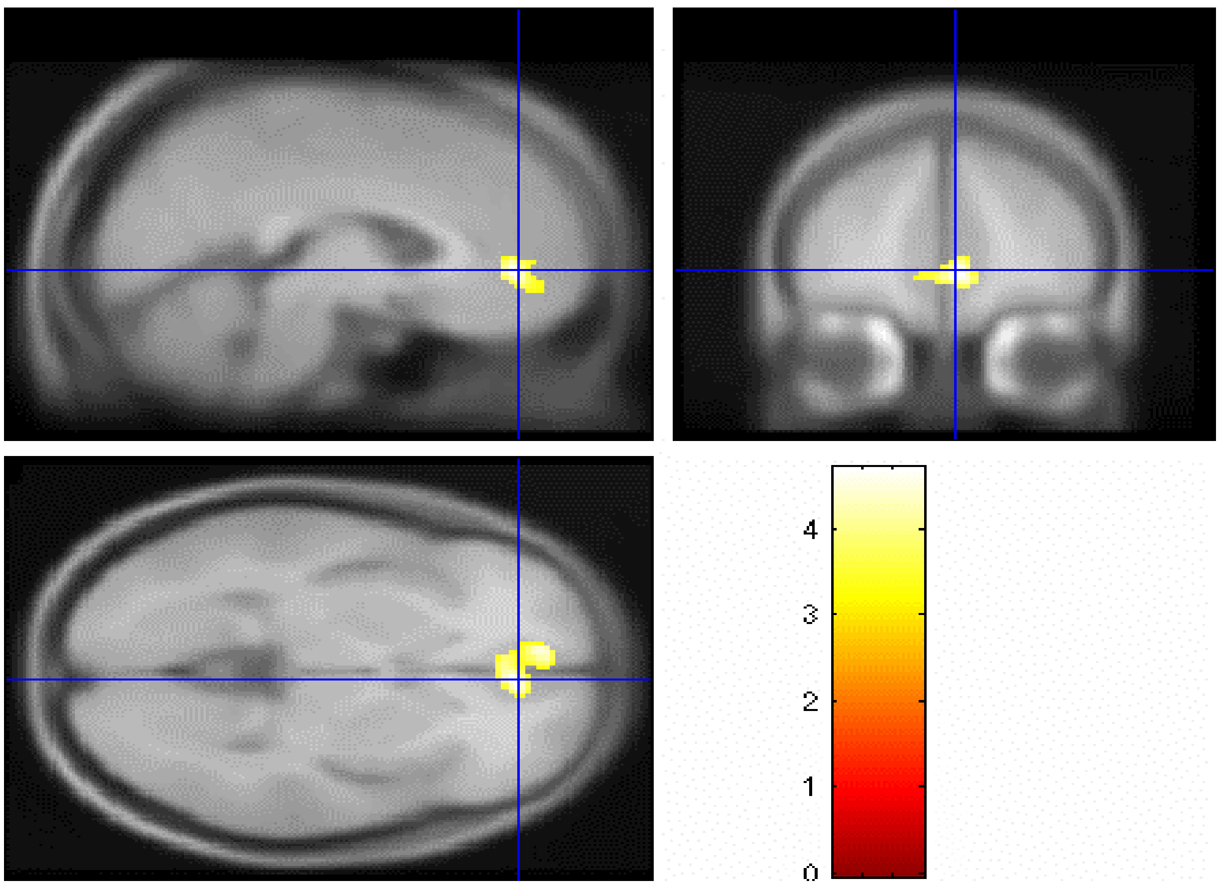
Ho et al *Molecular Psychiatry* (2005) **10**, 229.



Ohnishi et al (2006) Brain 129:399-410
Schizophrenics homozygous for the Val-COMT allele (n = 19) showed a significant reduction of volumes in the left parahippocampal gyrus, amygdala-uncus, ACC, left thalamus and the right MTG when compared to patients who carried the Met-COMT allele (n = 28).

Genetic imaging in the EHRS

HR differences for parametric contrast: COMT Met/Met<Val/Val

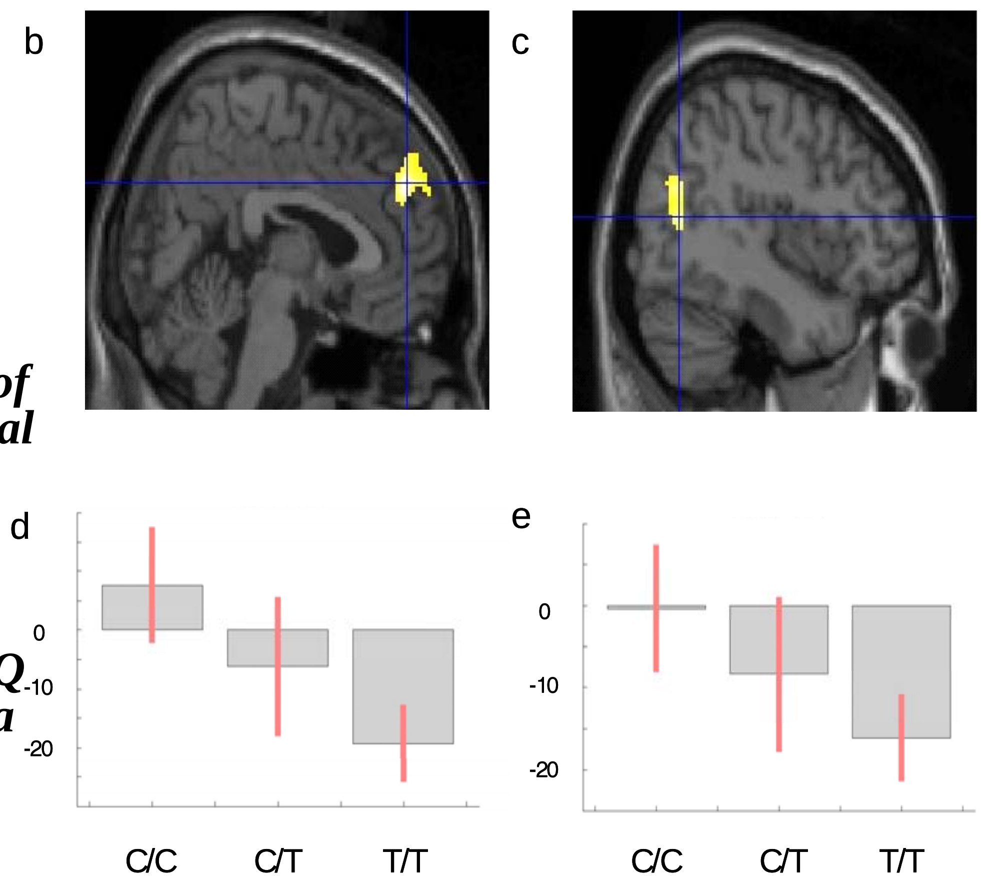


High Risk subjects with the COMT Val allele also had reduced grey matter density in anterior cingulate cortex and a greater risk of conversion

(McIntosh et al, Biol Psych 2007; 61:1127-34).

Neuregulin1 in the EHRS

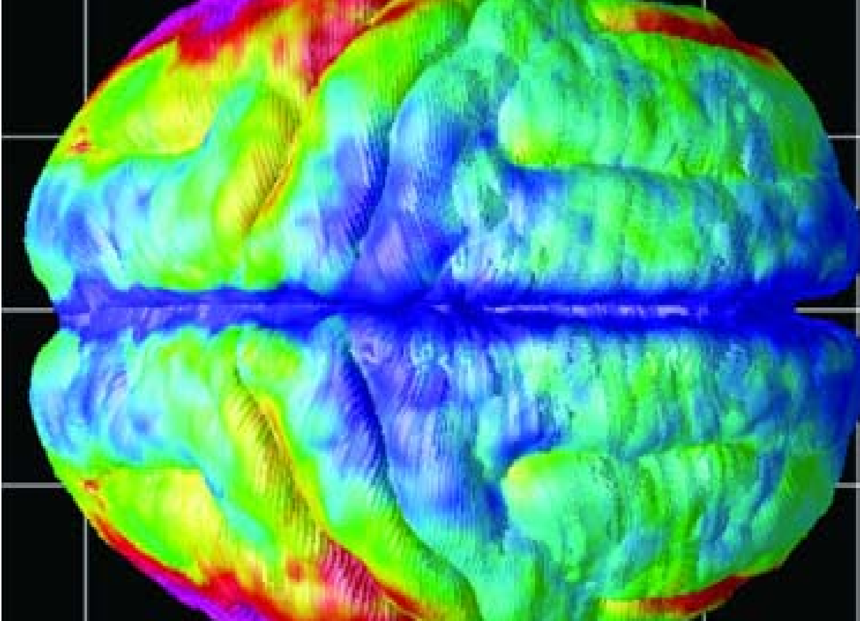
- Law et al (2006) reported that the risk allele of SNP8NRG243177, in the original disease-associated haplotype, alters binding sites for three transcription factors in a promoter region of NRG1 – increasing expression of the type IV transcript
- ***We found a highly significant effect of SNP8NRG243177 genotype on the development of psychotic symptoms in the EHRS cohort with 100% of individuals homozygous for the risk allele (T/T) developing psychotic symptoms at some time across the course of the study***
- ***Subjects with the risk (T/T) genotype showed significantly decreased activation of right medial PFC and right posterior medial temporal gyrus in the contrast of sentence completion versus rest***
- ***Using the National Adult Reading Test (NART), a measure of pre-morbid IQ, we found a significant effect of genotype on IQ which derived from the T/T group having a significantly decreased IQ***



Hall et al (2006) Nature Neuroscience 9:1477-8

Conclusions

- Schizophrenia is highly genetic and associated with PFC and MTL imaging abnormalities, which are also evident in relatives
- NRG1 may be associated with ‘trait’ effects of low IQ, abnormal fronto-temporal functioning and a liability to psychotic symptoms
- COMT is associated with PFC dysfunction on fMRI and reduced MTL volumes…and possibly with further reductions according to genetic background, with cannabis consumption and in patients



SCHIZOPHRENIA

FROM NEUROIMAGING TO NEUROSCIENCE

SCHIZOPHRENIA

FROM NEUROIMAGING TO NEUROSCIENCE

Neuroimaging techniques have made a huge contribution to our understanding of schizophrenia and other neuropsychiatric disorders. Until now, however, texts on both schizophrenia and neuroimaging have paid little attention to the overlap between these areas. This new volume is the first dedicated to unravelling how these techniques can help us better understand this complex disorder.

Each chapter focuses on a particular research method, describing the nature of the findings, the main technological problems, and future possibilities. Though including sufficient methodological detail to be of value to imaging researchers, the emphasis throughout is on providing information of value to clinicians.

Written and edited by leaders in schizophrenia research, this book details what structural and functional brain imaging studies have already established about schizophrenia and what developments are likely in the foreseeable future. It will be of great value to psychiatrists, neuropsychiatrists, and cognitive neuroscientists.

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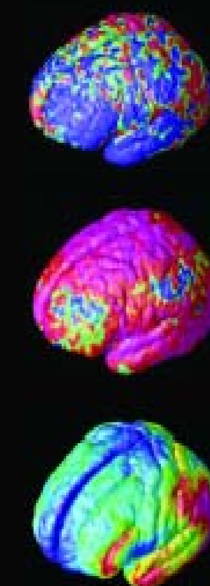

Brain Imaging of Childhood Abuse Related Posttraumatic Stress Disorder

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www.dougbremner.com
For copy of slides & disclosures

Disclosures

- Grant Support
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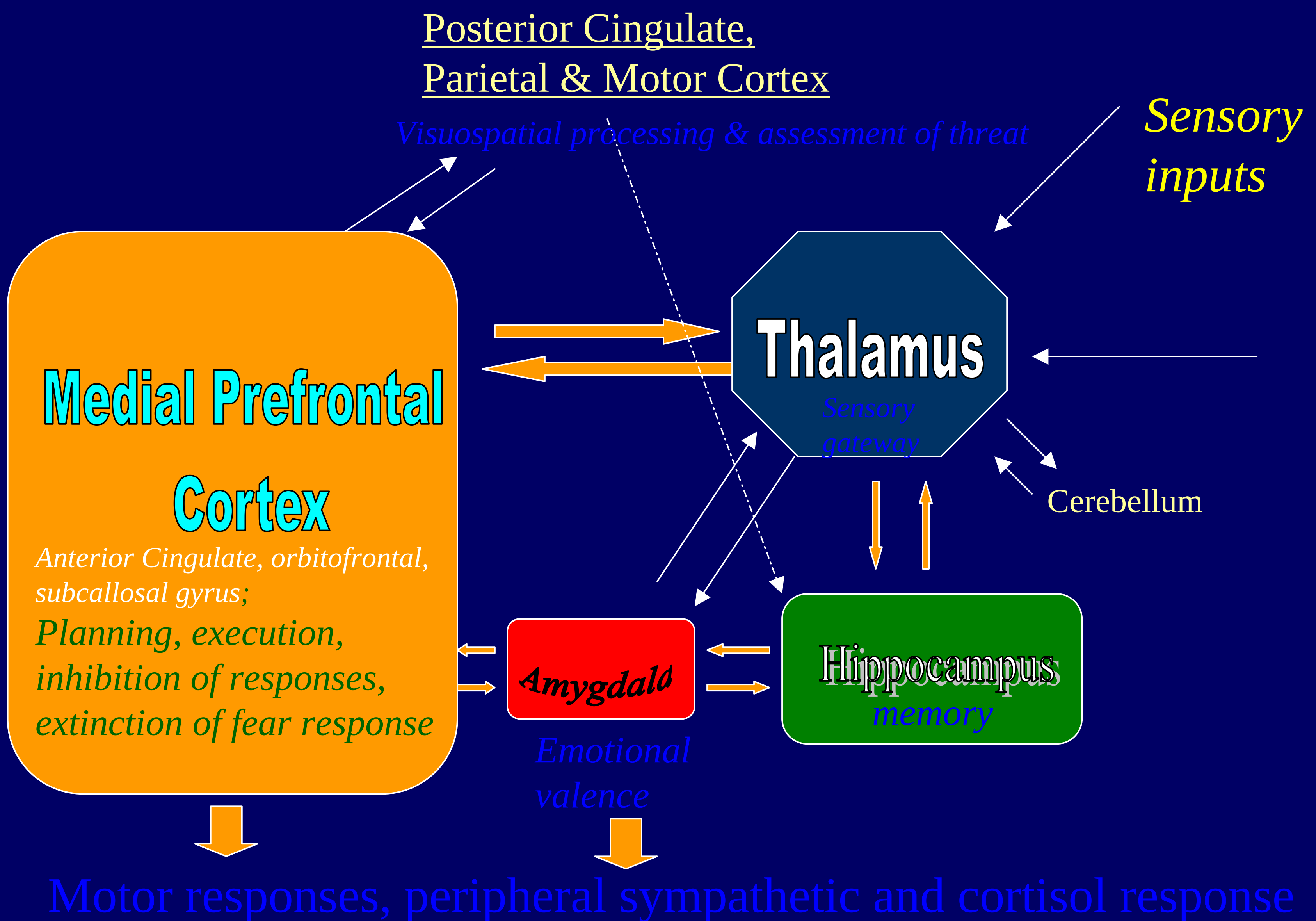
  (As co-investigator) R01 AG026255, R01 HL068630, R01 HL703824, R01 MH068791, P50 MH58922
- Veterans Administration: Merit Review, VET-HEAL Award
- National Alliance for Research on Schizophrenia and Depression (NARSAD) Independent Investigator Award
- American Foundation for Suicide Prevention (AFSP)
- Georgia Research Alliance
- GlaxoSmithKline Investigator Initiated Medical Research

- Consulting
- Novartis
- GlaxoSmithKline
- Speakers Bureaus
- None
- Discussion of Off Label Medication Use
- Phenytoin

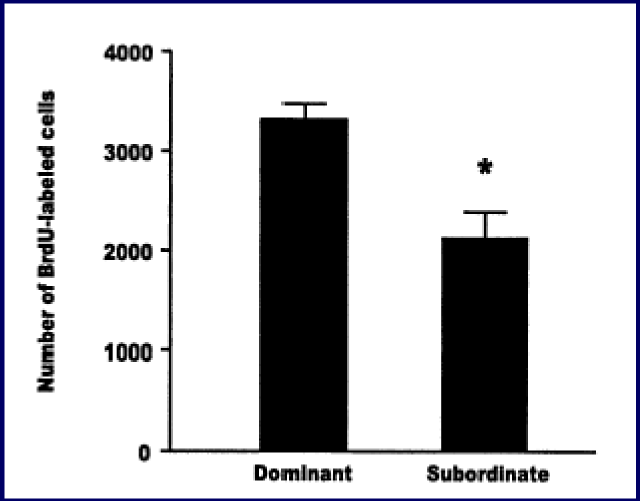
Posttraumatic Stress Disorder

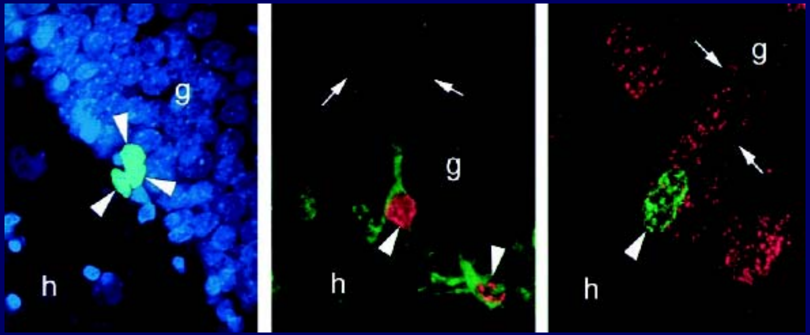
- Intrusive memories, nightmares, flashbacks, arousal, avoidance, startle, sleep disturbance, gaps in memory and concentration
- Associated with threat to life or other with fear/horror/helplessness (A)
- Affects 15% of traumatized individuals
- 16% of women with sexual abuse
- 8% lifetime PTSD prevalence (10% women)
- Abuse also associated with borderline personality disorder (BPD) and dissociative identity disorder (DID)

Functional Neuroanatomy of Trauma Spectrum Disorders



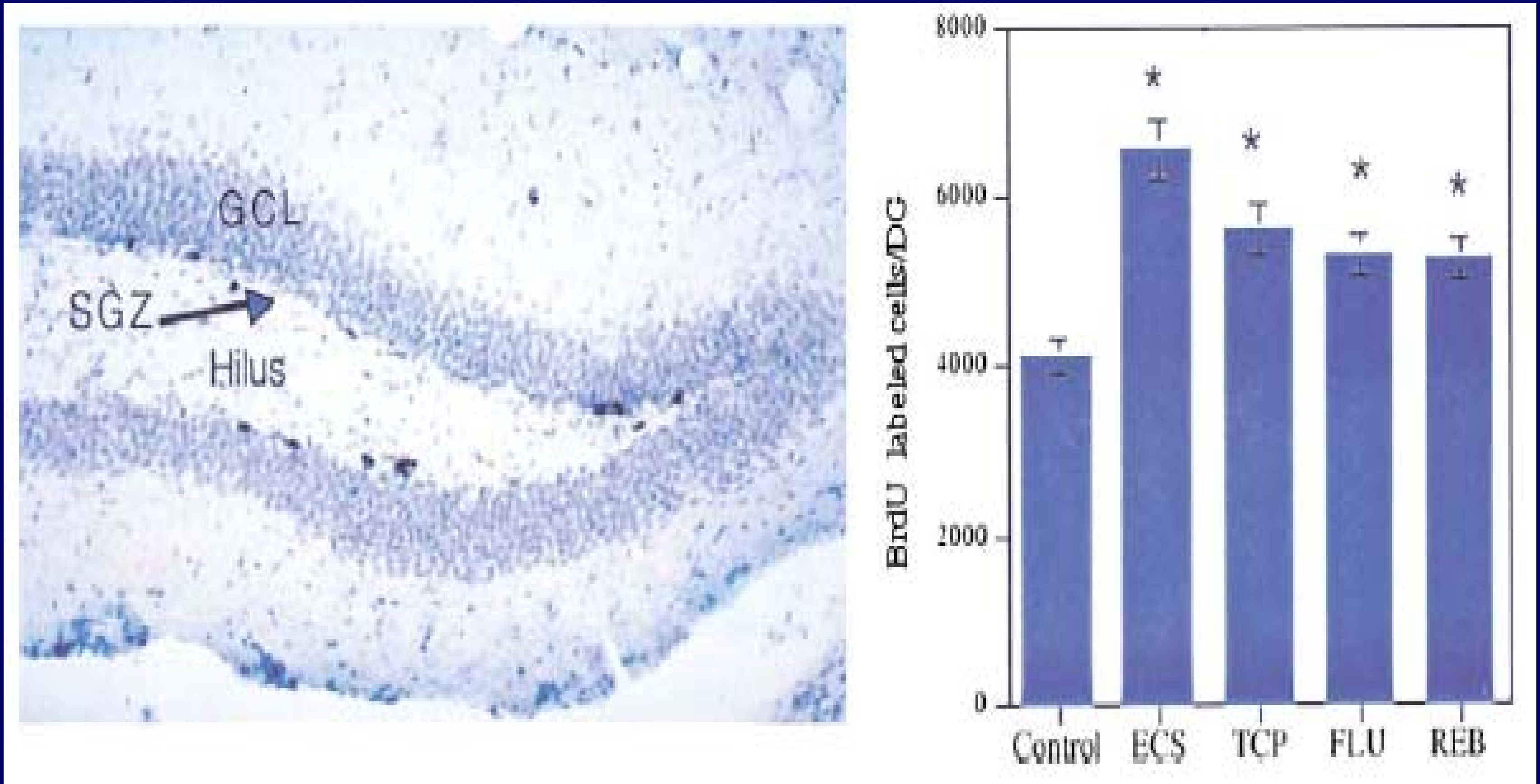
Stress Results in Decreased Hippocampal Neurogenesis





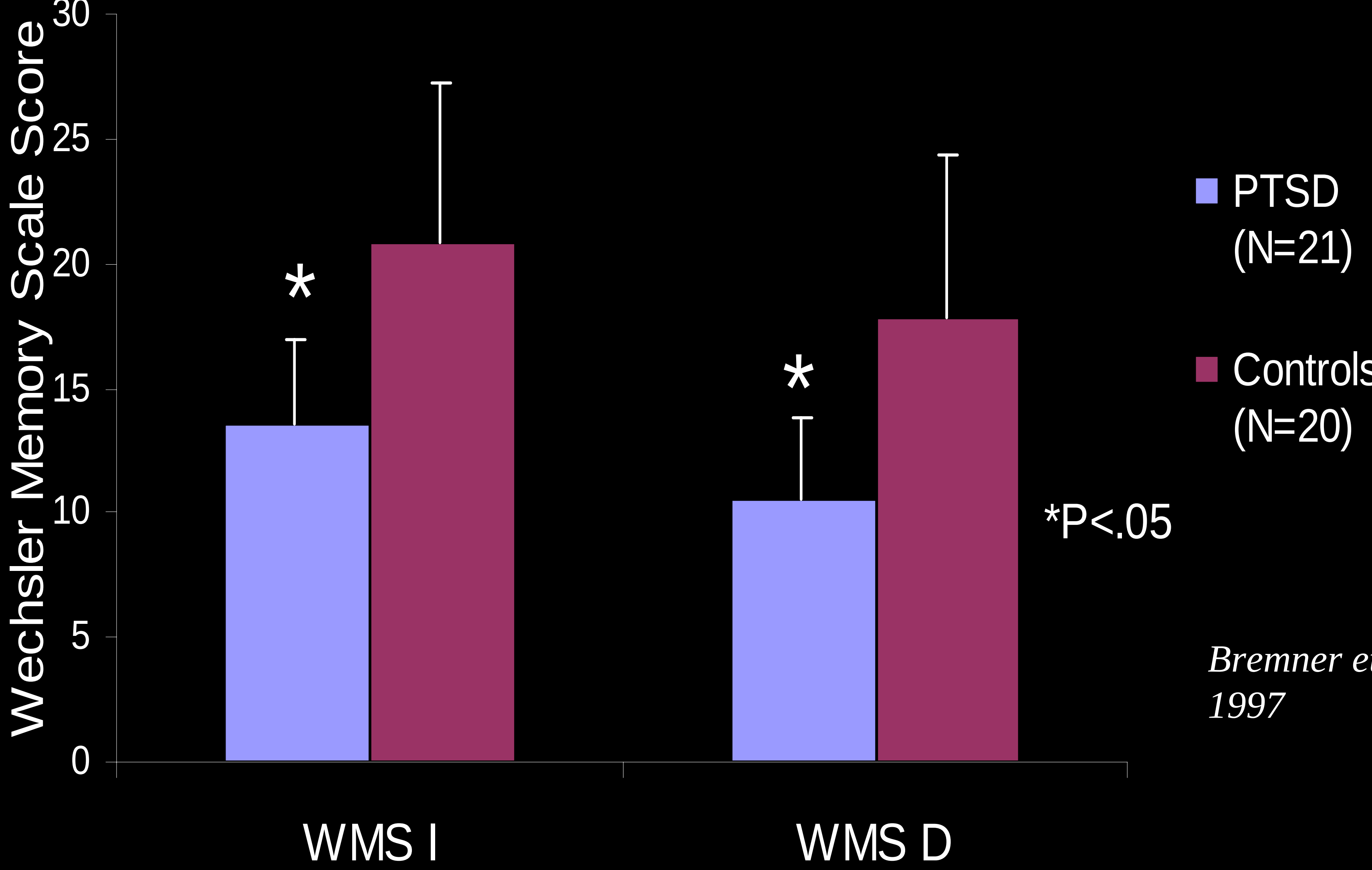
Gould et al 2002

Antidepressant Treatments Promote Hippocampal Neurogenesis



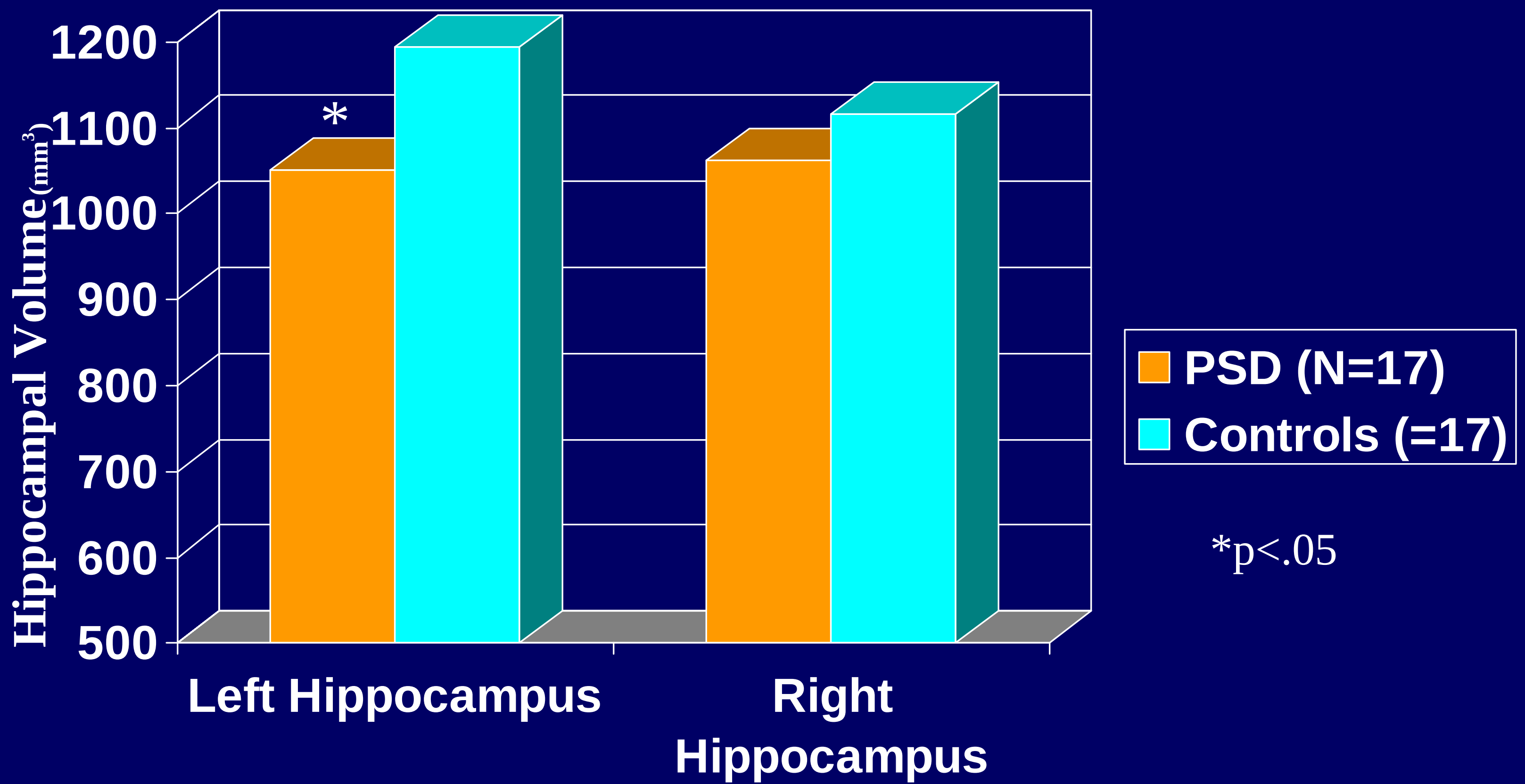
Duman et al 2002

Verbal Memory Deficits in Childhood Abuse-related PTSD



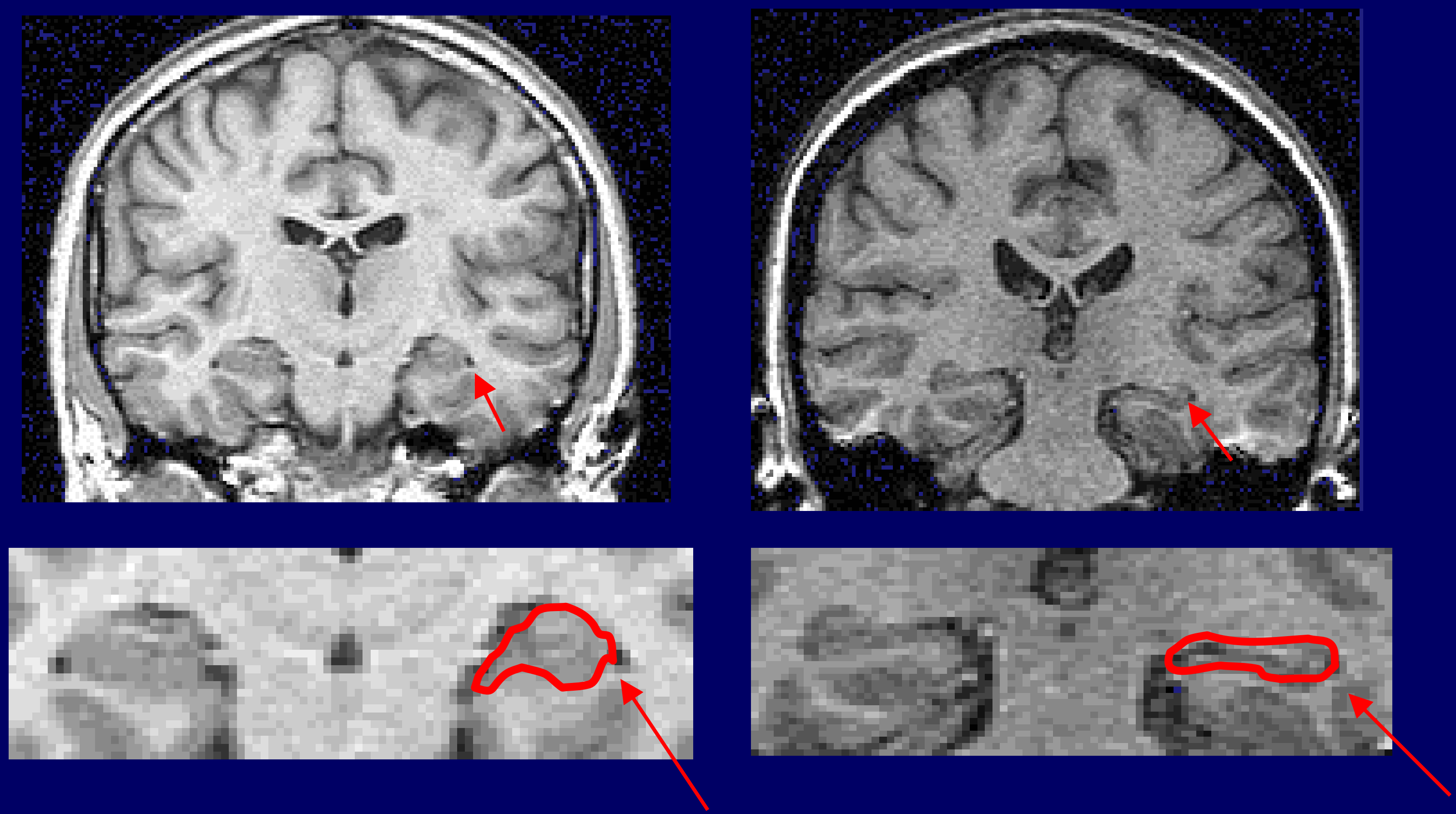
Bremner et al 1997

Hippocampal Volume Reduction in Childhood Abuse-related PTSD



12% reduction in left hippocampal volume in abuse-related PTSD

Hippocampal Volume Reduction in PTSD



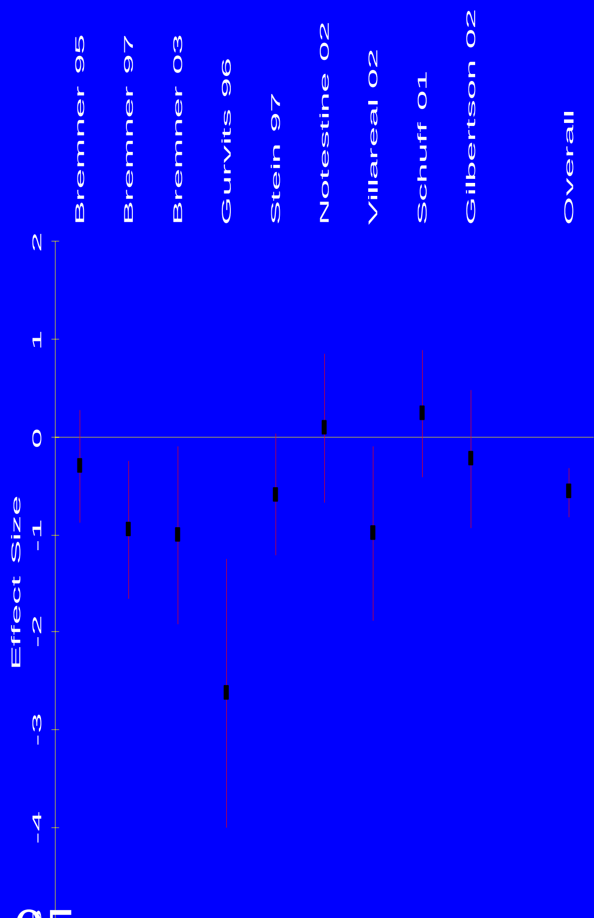
NORMAL **PTSD**

Bremner et al., Am. J. Psychiatry 1995; 152:973-981.
Bremner et al., Biol. Psychiatry 1997; 41:23-32.
Gurvits et al., Biol Psychiatry 1996;40:192-199.
Stein et al., Psychol Med 1997;27:951-959. DeBellis 1999-no change in children with PTSD

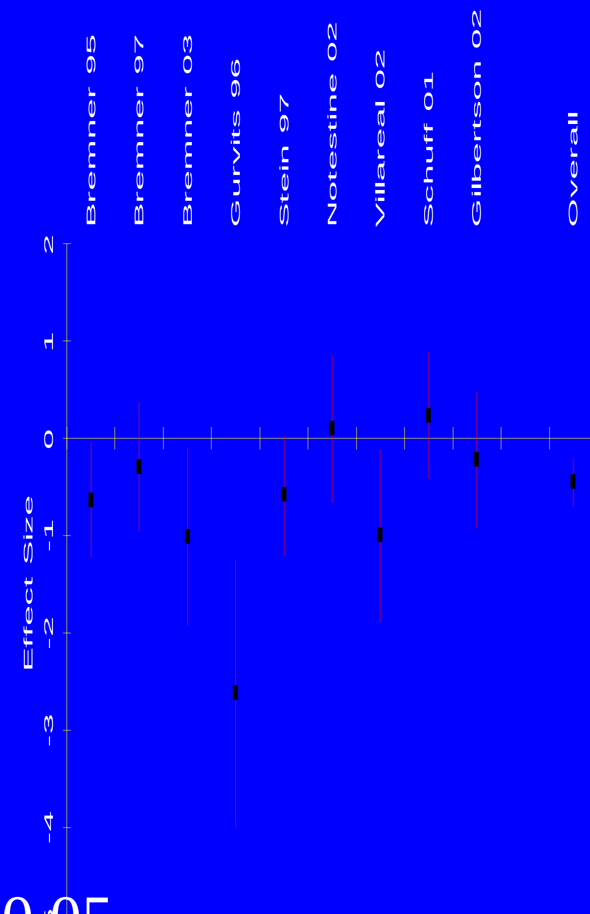
J Douglas Bremner, MD, Emory University

Effect Size Estimates for Hippocampal Volume in Adults with Chronic PTSD Versus Healthy Subjects

Pooled meta-analysis demonstrates smaller hippocampal volume in PTSD



P<0.05

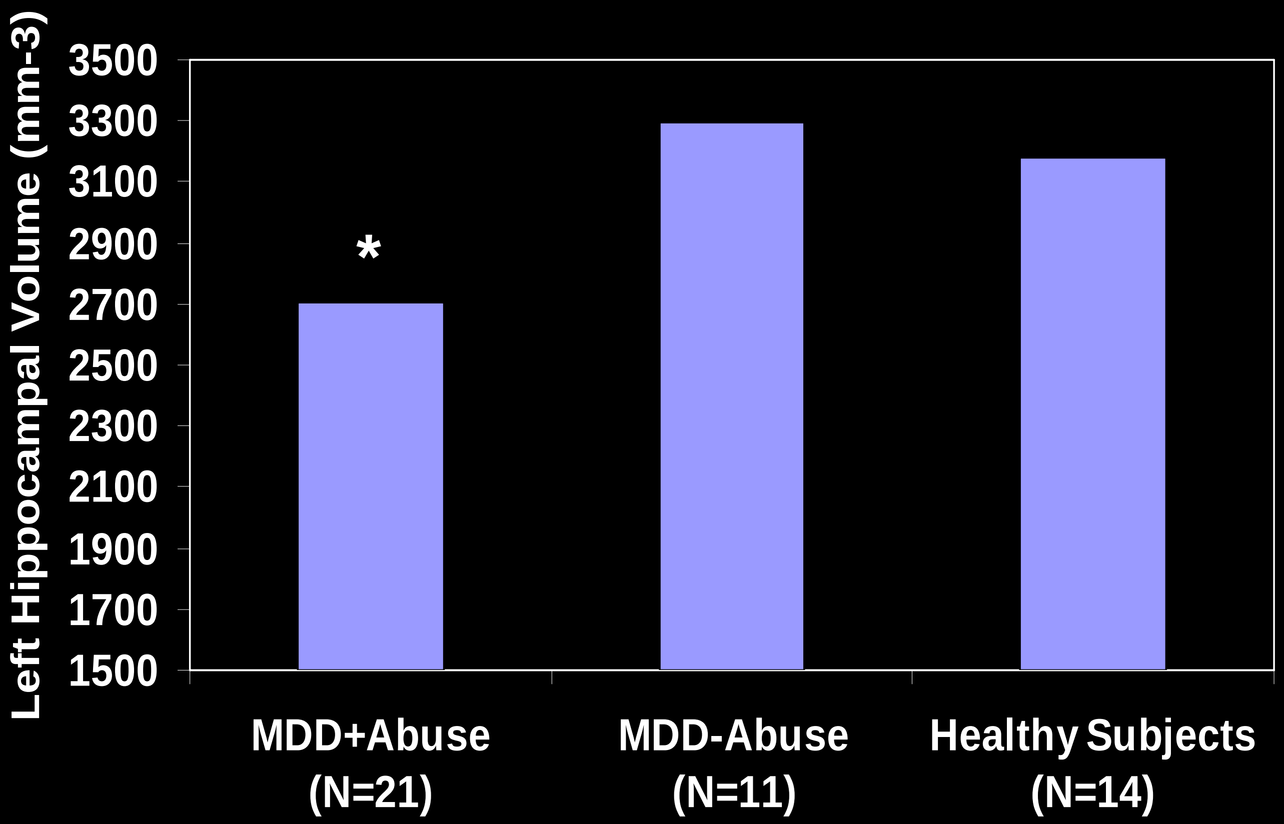


P<0.05

Left Hippocampus

Right Hippocampus

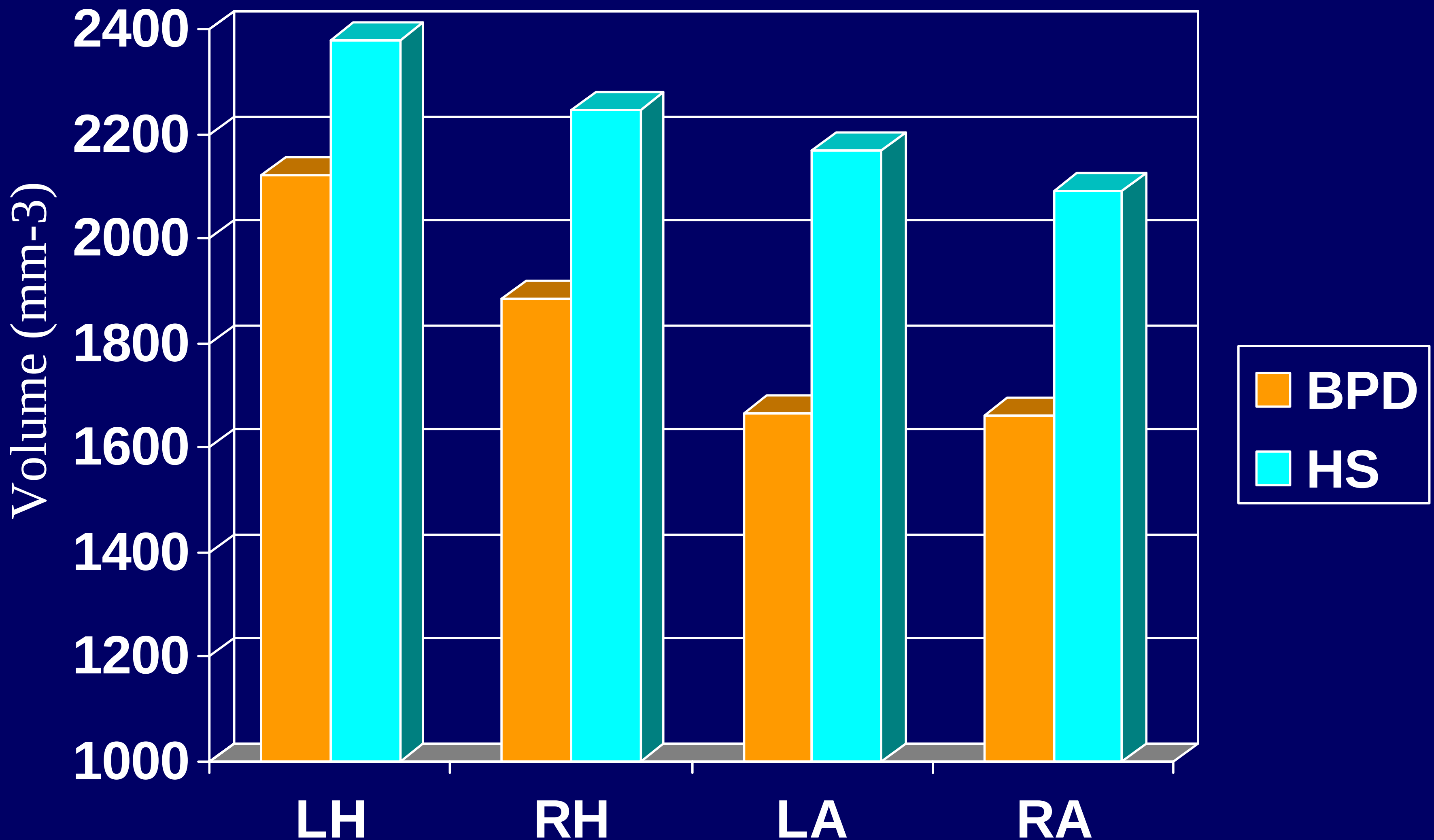
Smaller Hippocampal Volume in Women with Childhood Abuse and Depression



Vythilingam et al.,Am J Psychiatry, 2002

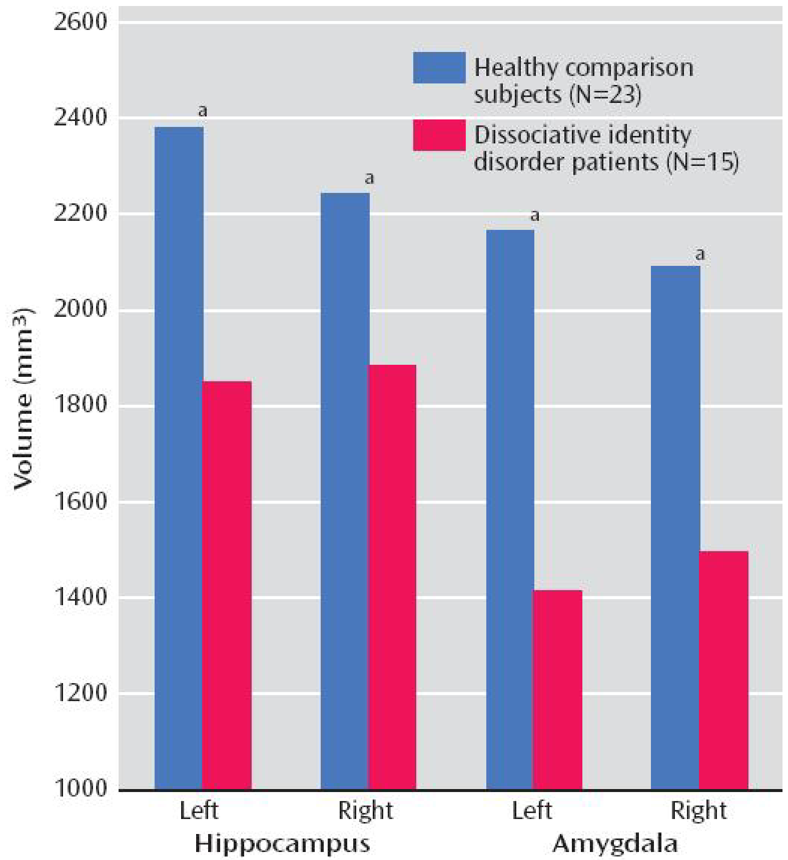
*p<.05

Smaller Hippocampal and Amygdala Volume in Abused Women with BPD



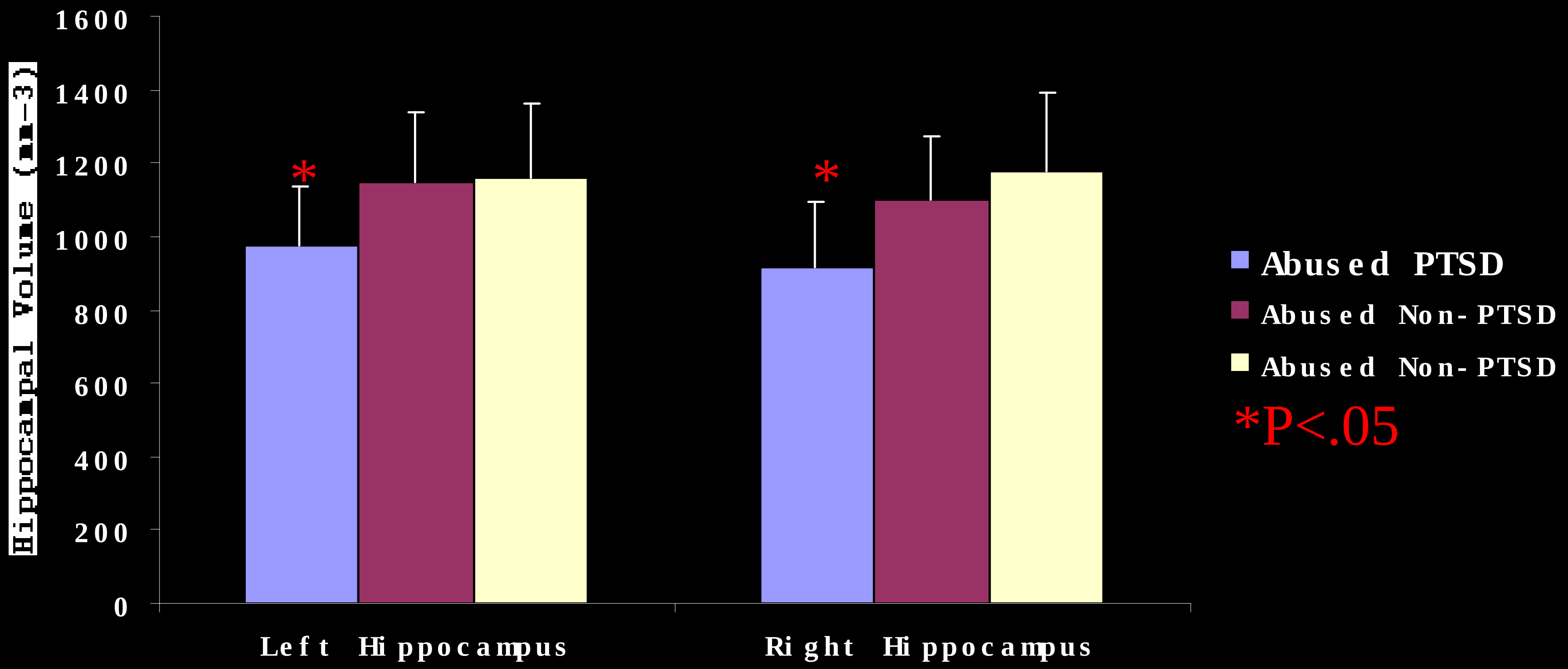
Schmahl et al., unpublished

Smaller Hippocampal Volume in Abused Women with Dissociative Identity Disorder



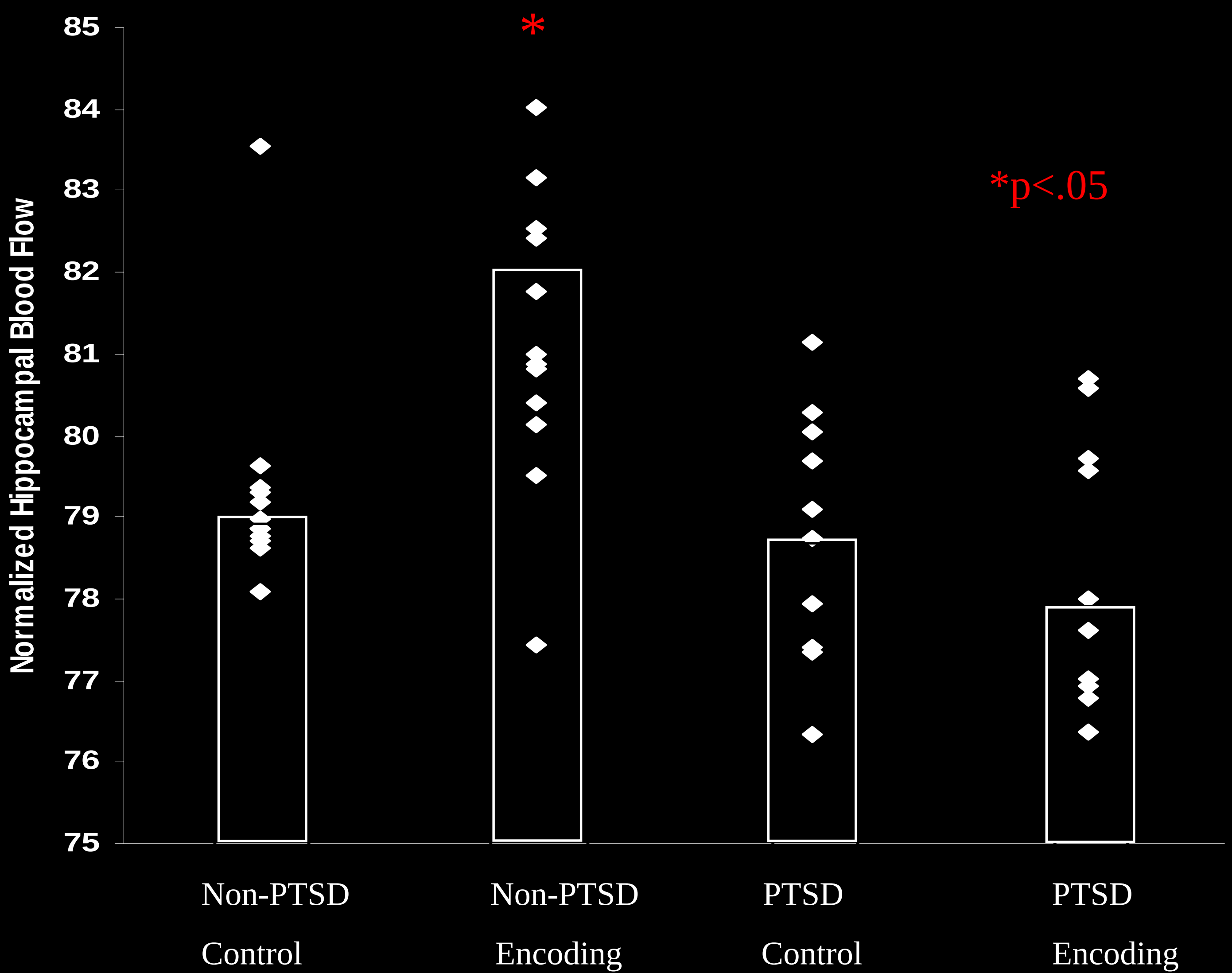
[a] Significant difference between groups ($p<0.05$, t test for nonpaired samples).

Smaller Hippocampal Volume in Women with Early Childhood Sexual Abuse-related PTSD



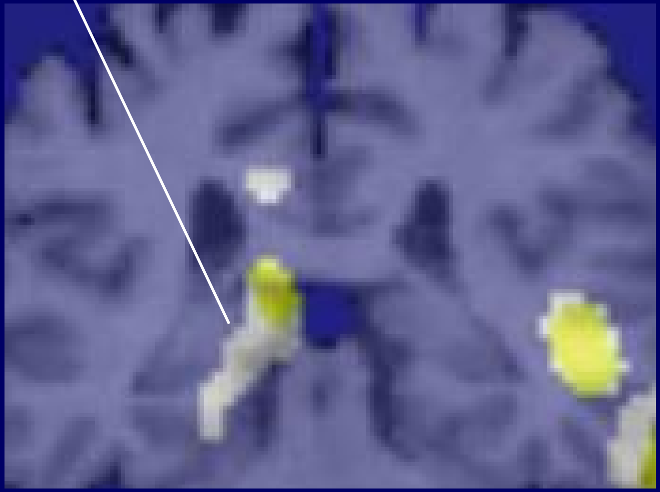
Hippocampal Volume measured with Magnetic Resonance Imaging (MRI)
Bremner et al Am J Psychiatry 2003

Failure of Hippocampal Activation with Memory Encoding in Women with Abuse-related PTSD



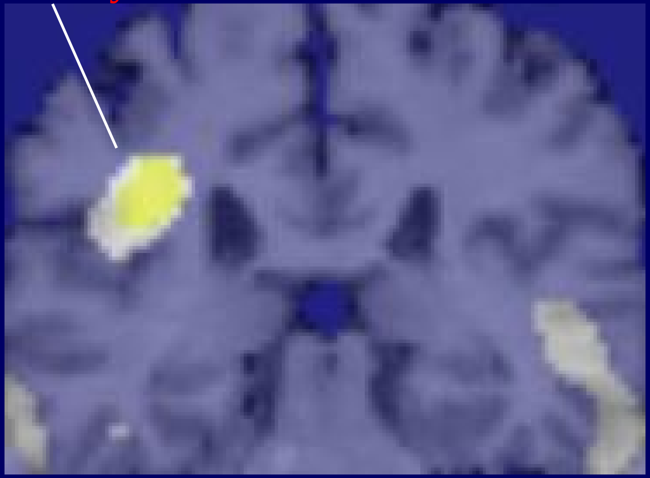
Failure of Hippocampal Activation in Women with PTSD Related to Childhood Sexual Abuse

Left Hippocampus Region



Abused Non-PTSD
Women (N=12)

L. Inferior
Frontal Gyrus



Abused PTSD
Women (N=10)

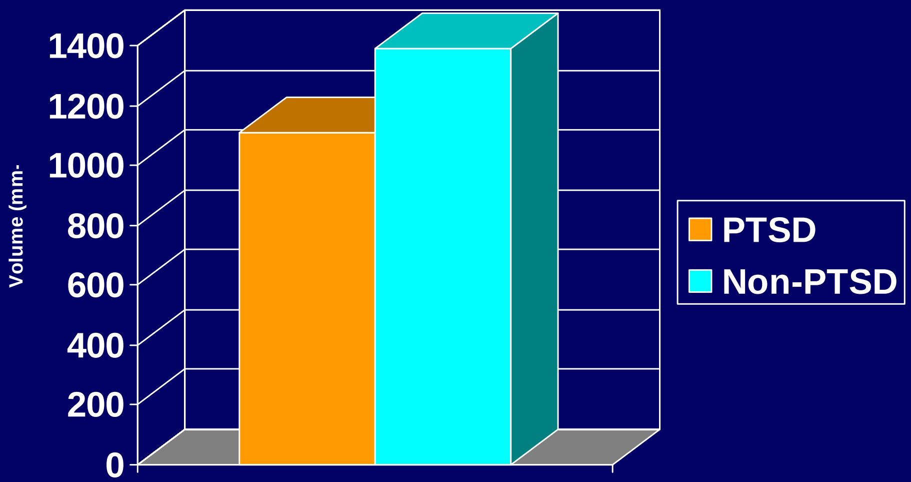
Increased blood flow during encoding of paragraph relative to control condition

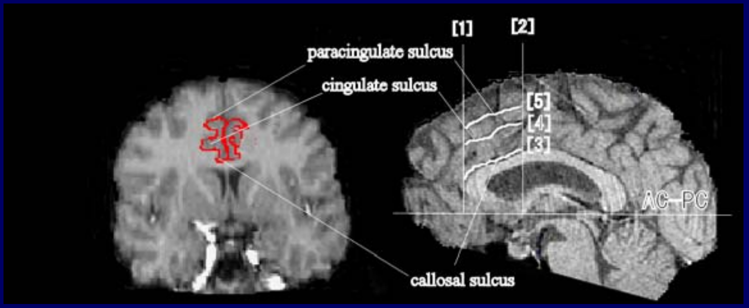
Statistical parametric maps overlaid on MR (z score>3.09; p<.001)

Trauma and the Medial Prefrontal Cortex

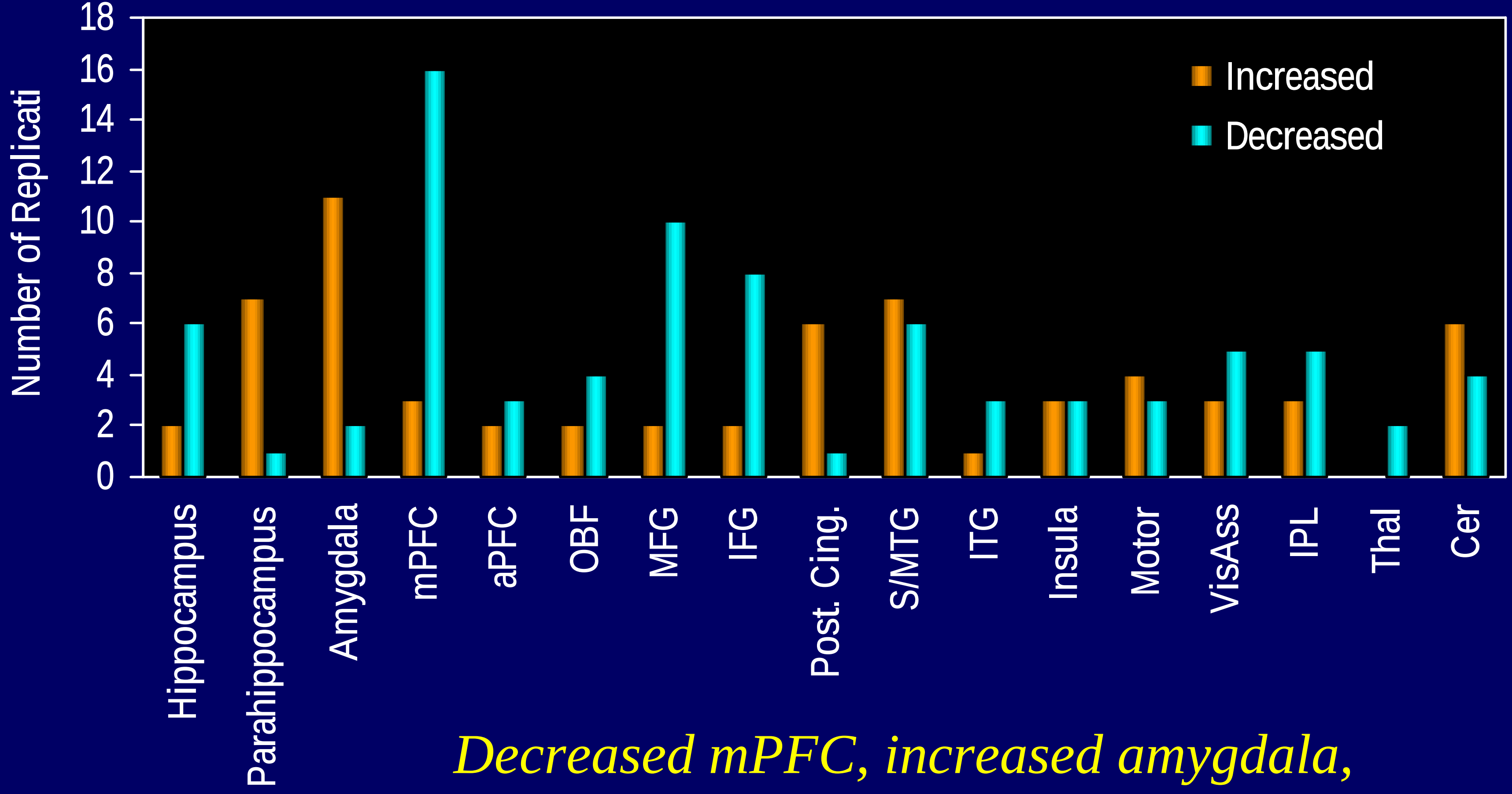
- Medial prefrontal cortex involved in inhibition of fear responses in the amygdala (Quirk)
- Early stress associated with decreased dendritic branching in medial prefrontal cortex (Radley)
- Neurological damage associated with deficits in emotional responding (includes orbitofrontal cortex and anterior cingulate)

Decreased Anterior Cingulate Volume in Women with Abuse Related PTSD



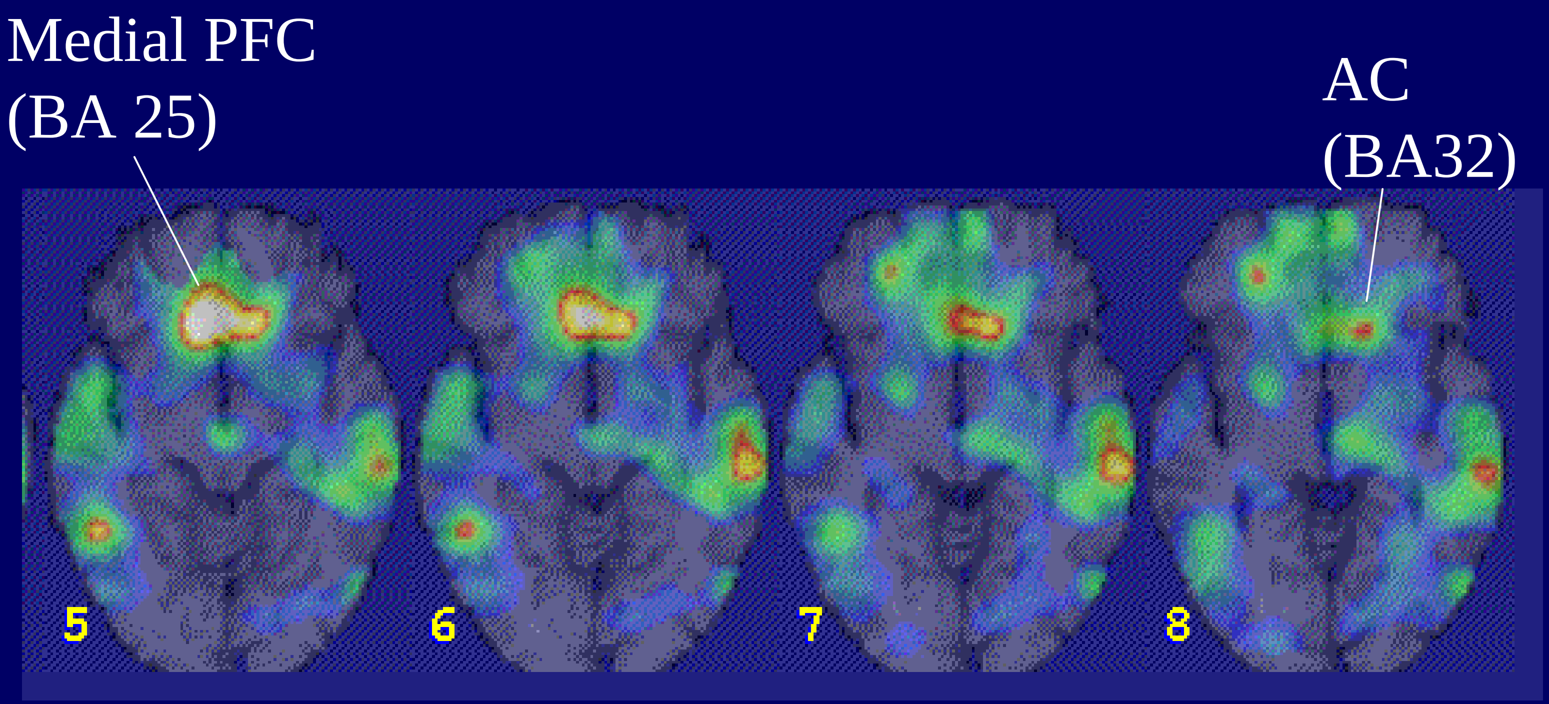


Replications of Findings from Functional Imaging in PTSD



Decreased mPFC, increased amygdala, decreased DLPFC & hippocampus

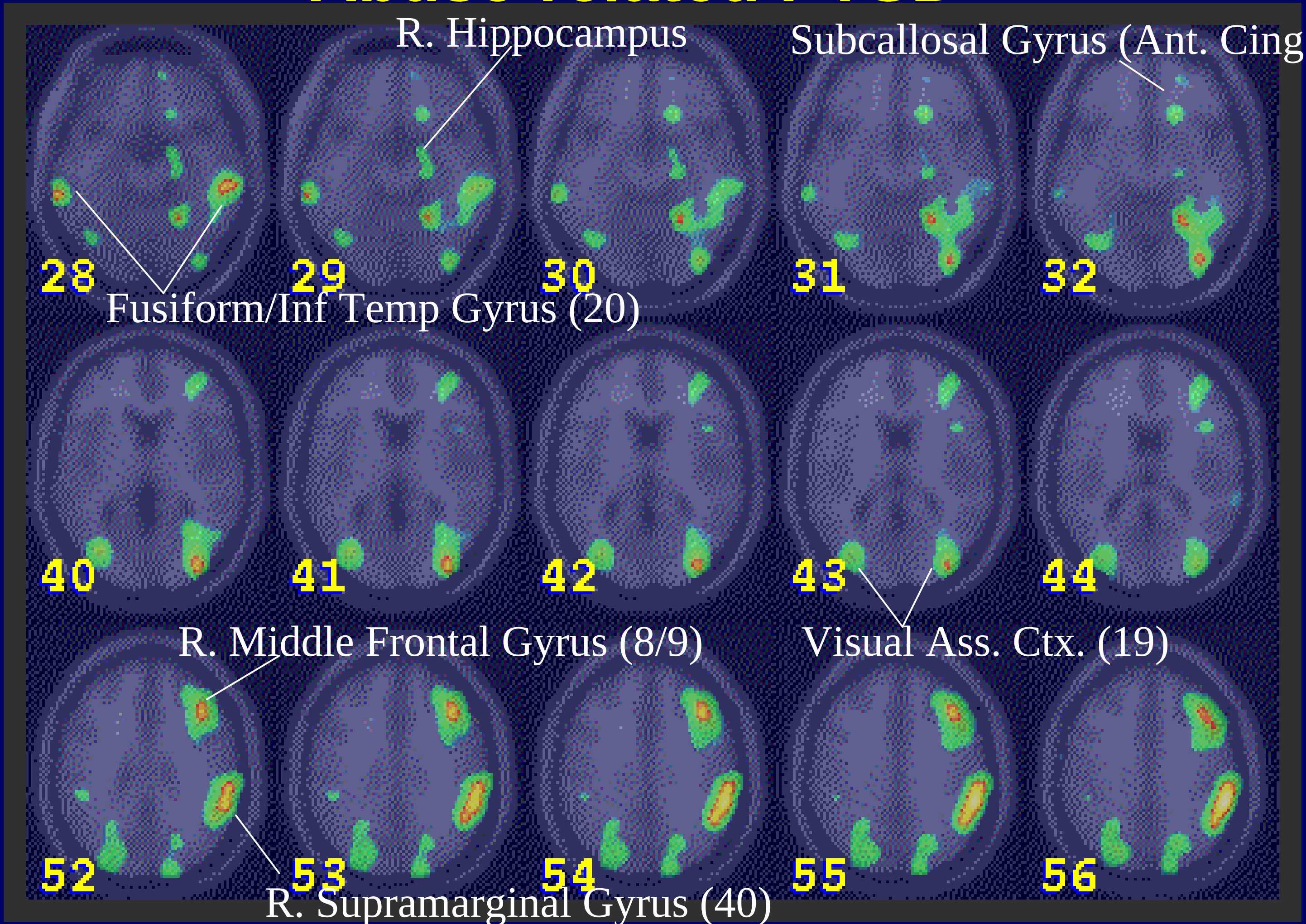
Medial Prefrontal Cortical Dysfunction with Traumatic Memories in PTSD



Decreased function in medial prefrontal cortical areas
Anterior Cingulate BA 25, BA 32 in veterans with PTSD compared to
Veterans without PTSD during viewing of combat-related slides & sounds
Z score >3.00; p<.001

Bremner et al Biol Psychiatry 1999

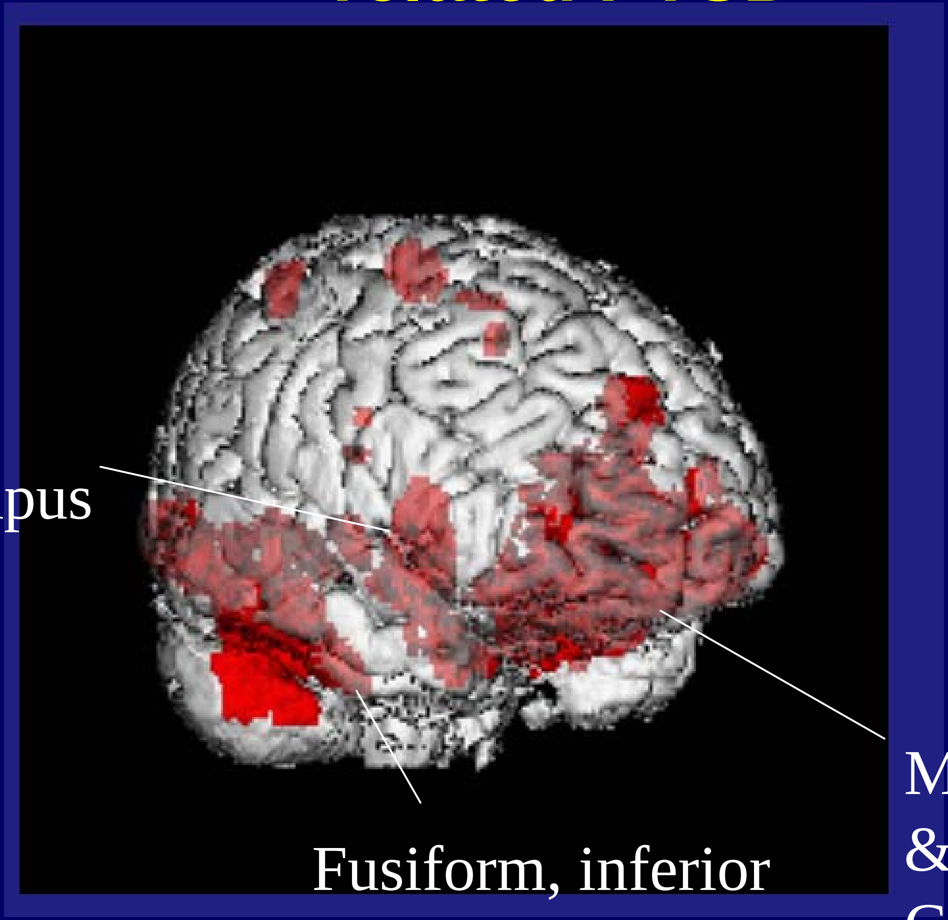
Decreased Blood Flow during Memories of Abuse in Women with Childhood Sexual Abuse-related PTSD



Areas displayed with z score>3.00; p<.001

Bremner et al Am J Psychiatry 1999

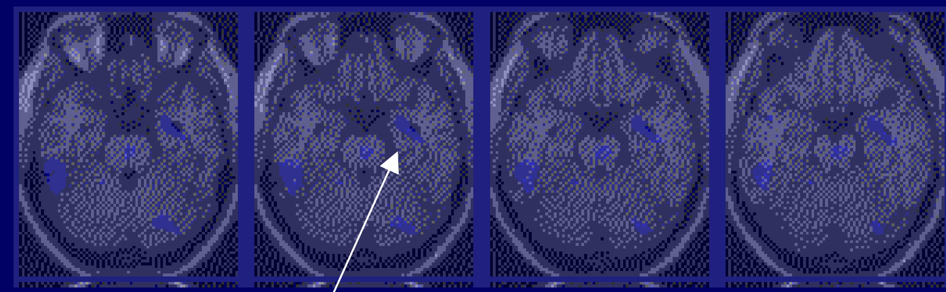
Decreased Blood Flow During Recall of Emotionally Valenced Words in Abuse-related PTSD



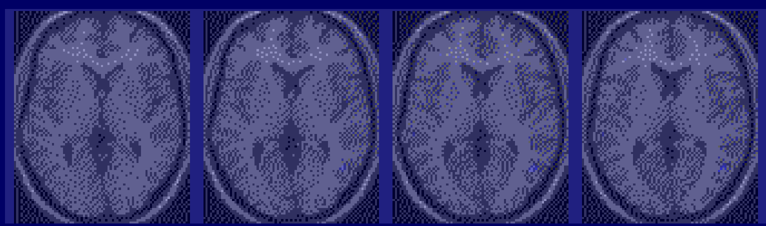
Retrieval of Word pairs like "blood-stench"

Bremner et al Biol Psychiatry 2004

Decreased Blood Flow with Emotional Stroop in Abused Women with and without PTSD



R. Hippocampus

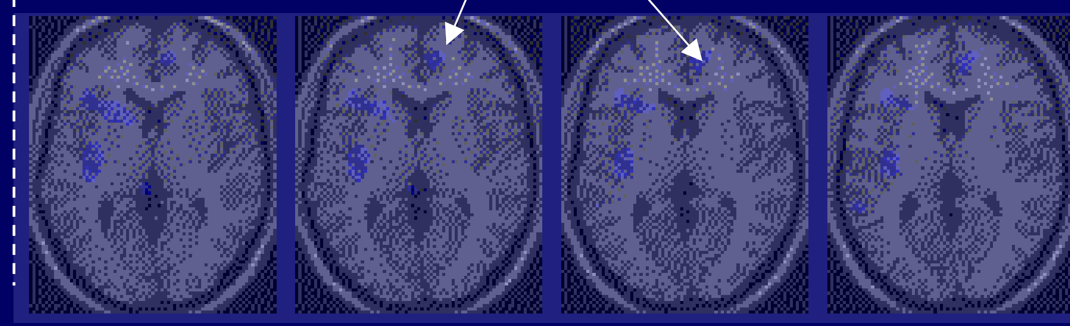


Abuse Controls

Emotional stroop: say the color of the word rape

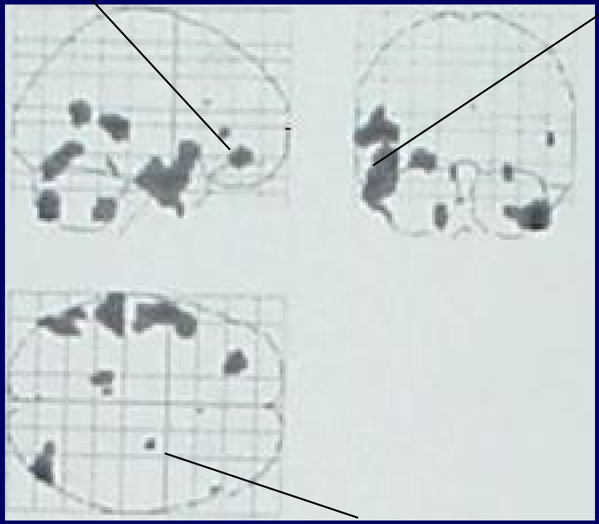
Anterior Cingulate (32,24)

PTSD



Blue areas represent areas of relatively greater decrease in blood flow, emotional v neutral stroop, z>3.09; p<0.001; Bremner et al Biol Psychiatry 2004

Neural Correlates of Memories of Abandonment in Borderline Personality Disorder with Early Trauma



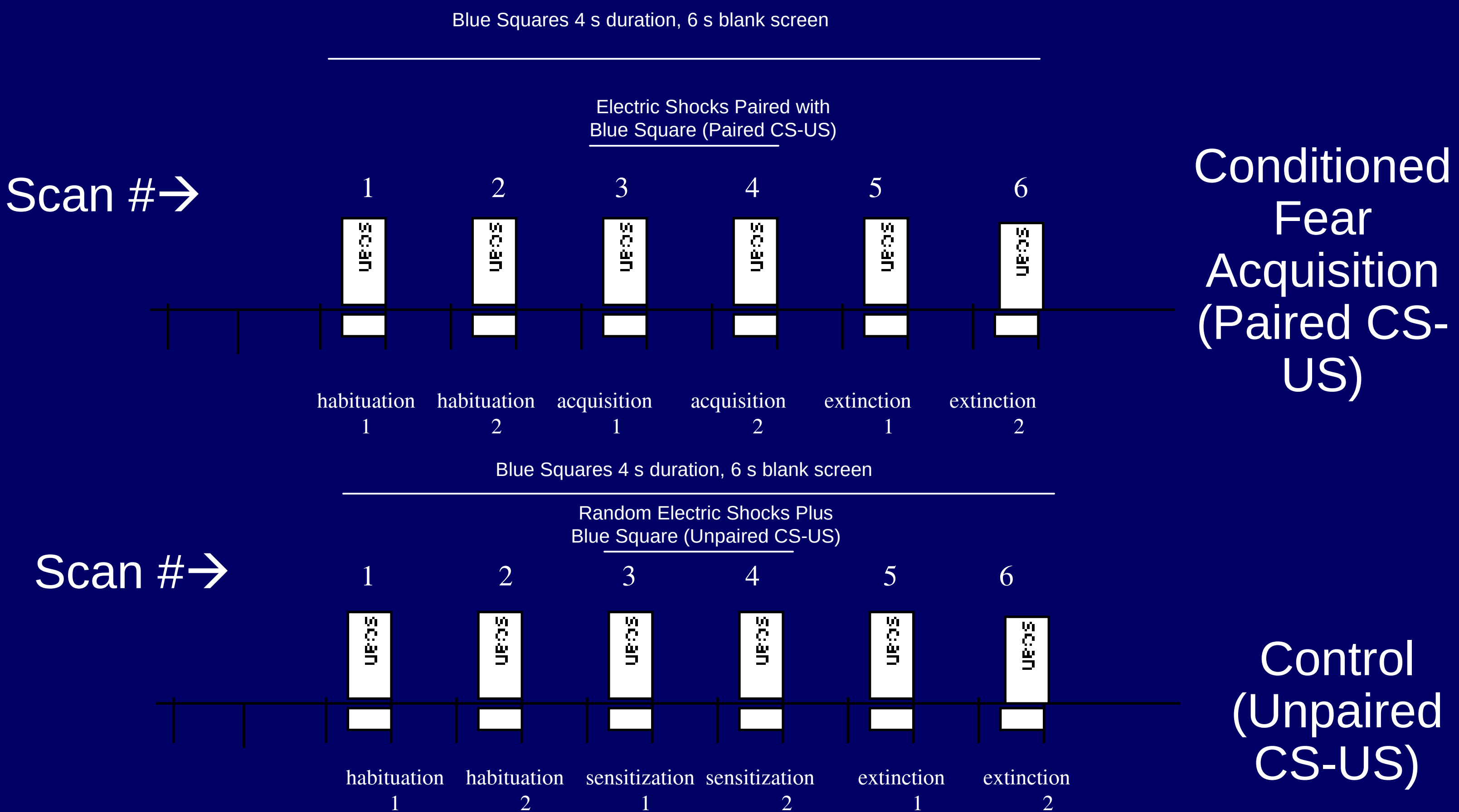
Areas of decreased Blood flow during Reading of script Of an abandonment Situation v control

Schmahl et al., Biol Psychiatry 2003

Conditioned Fear in PTSD

- Pairing of light and shock leads to increased fear responding and increased startle to light alone (conditioned fear)
- Conditioned fear and startle response mediated by central nucleus of the amygdala
- Failure of extinction with lesions of medial prefrontal cortex (inhibits amygdala)
- Study design– habituation (blue square), fear acquisition (blue square + shock), extinction (blue square); control day– random shocks

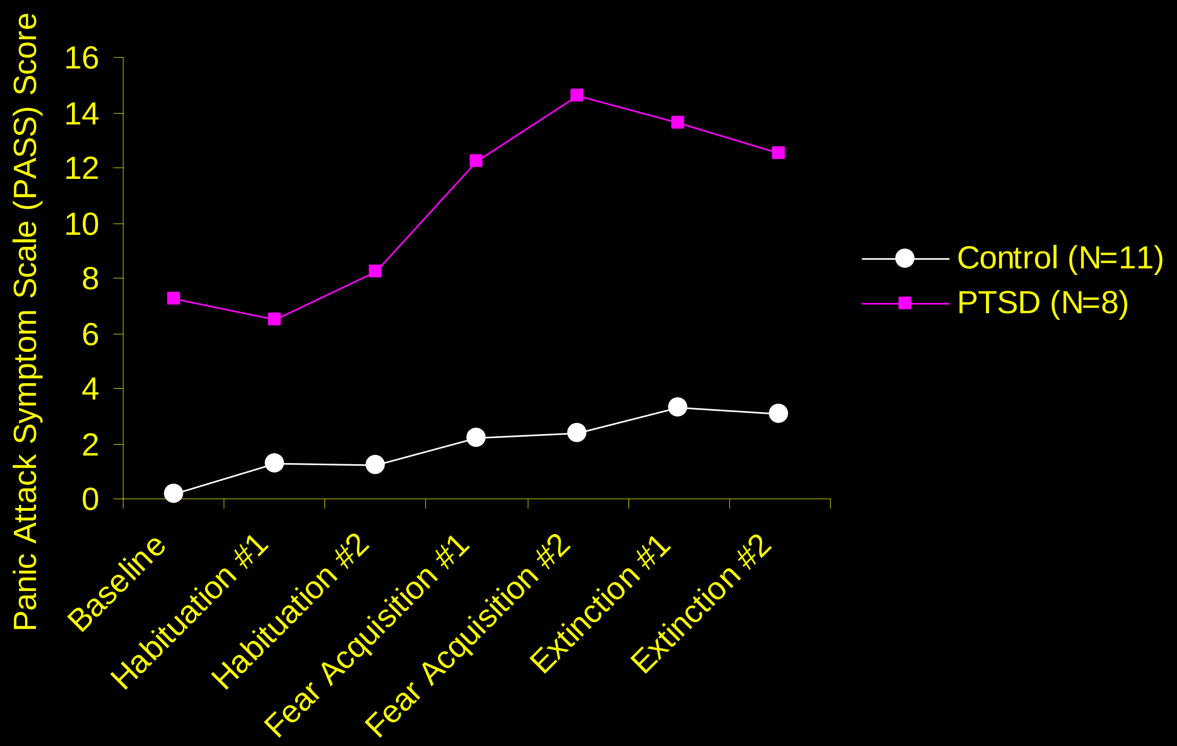
Fear Conditioning in PTSD Study Design



Conditioned Stimulus (CS)=Blue Square

Unconditioned Stimulus (US)=Electric Shock

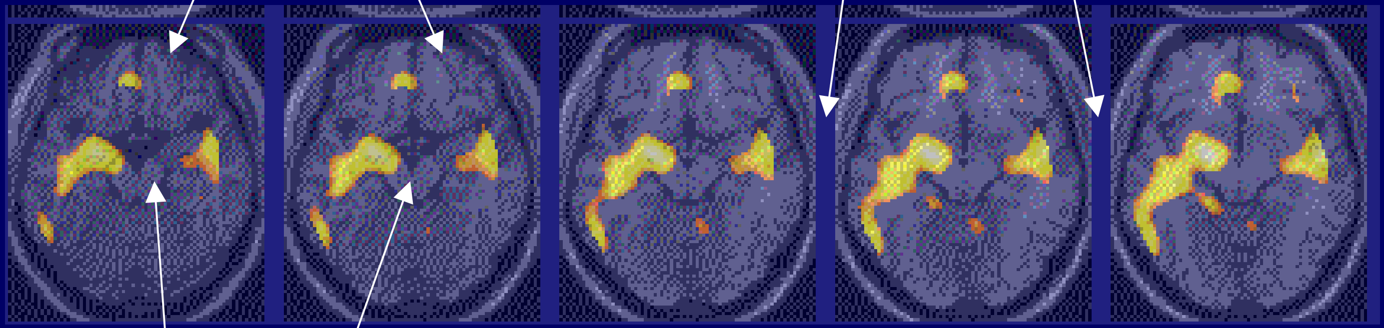
Increased Anxiety Symptoms with Fear Acquisition and Extinction in Abuse-related PTSD



Increased Blood Flow with Fear Acquisition versus Control in Abuse-related PTSD

Orbitofrontal Cortex

Superior Temporal Gyrus



Left Amygdala

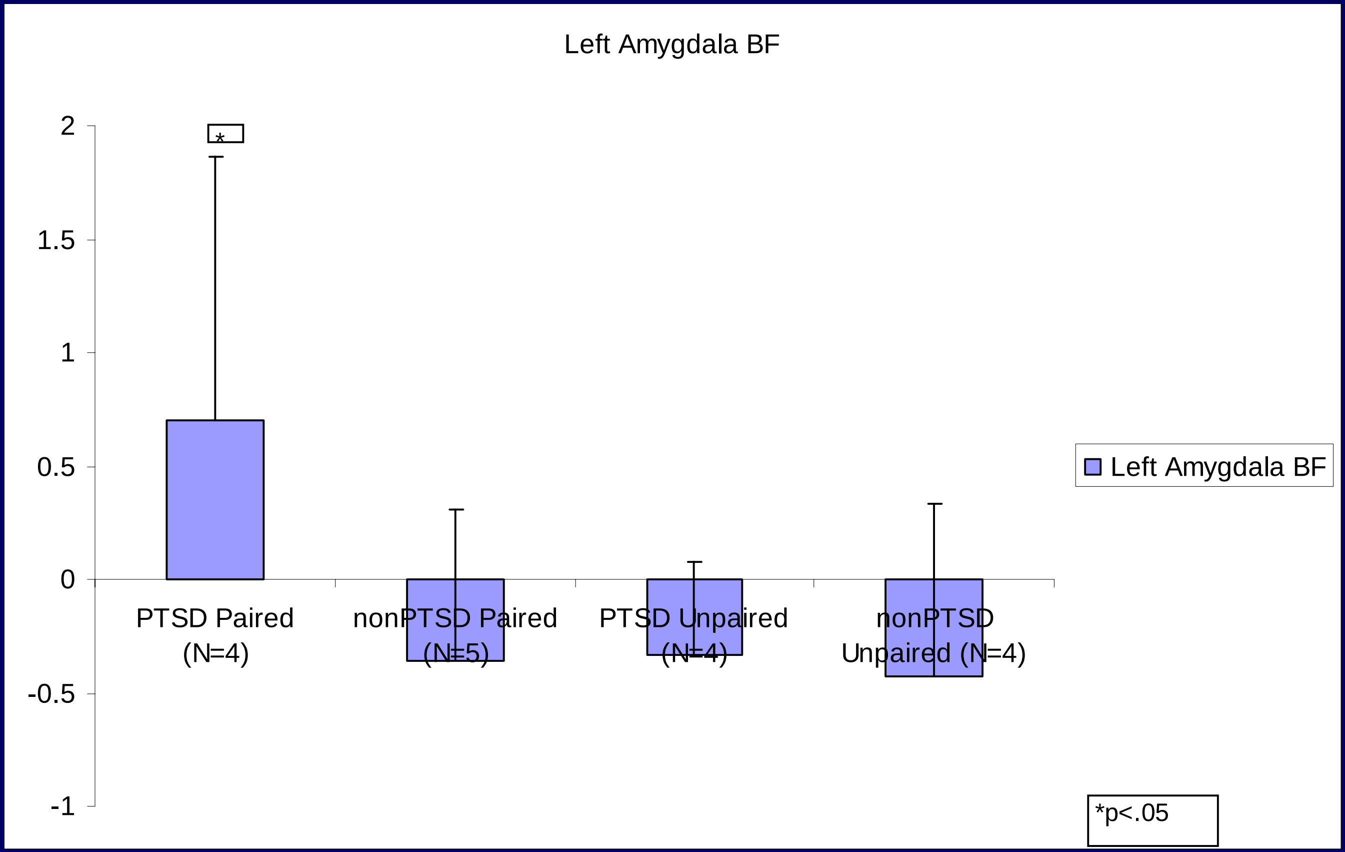
Yellow areas represent areas of relatively greater increase in blood flow with paired vs. unpaired US-CS in PTSD women alone, $z>3.09$; $p<0.001$

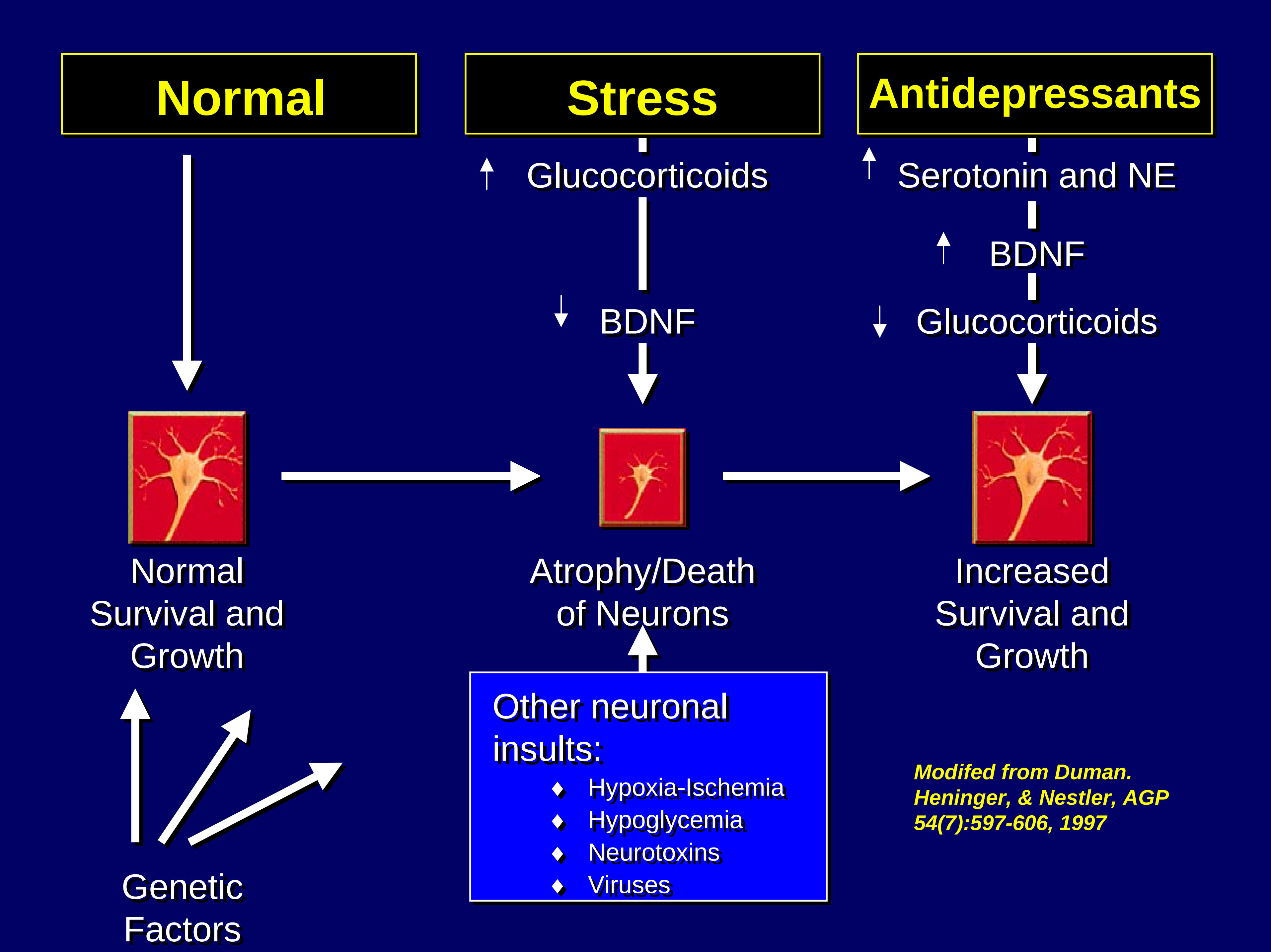
Bremner et al Psychol Med 2005

Increased Amygdala Activation in PTSD

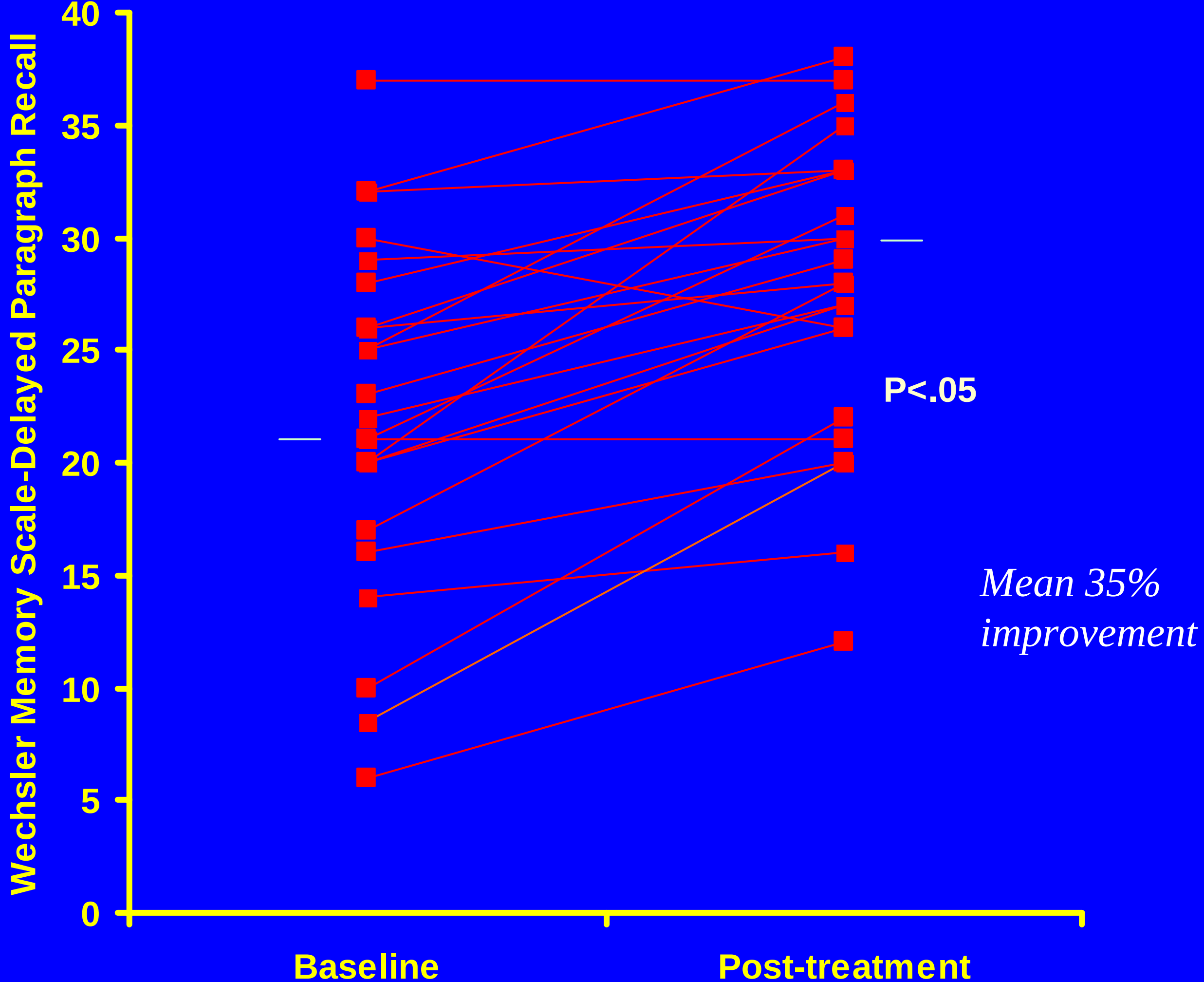
- fMRI in conjunction with fear conditioning
- Neutral faces used as conditioned stimulus (CS); random interval between CS
- Unconditioned stimulus (shock) presented at end of CS presentation
- Second group received unpaired CS-UCS

Increased Amygdala Activation in PTSD



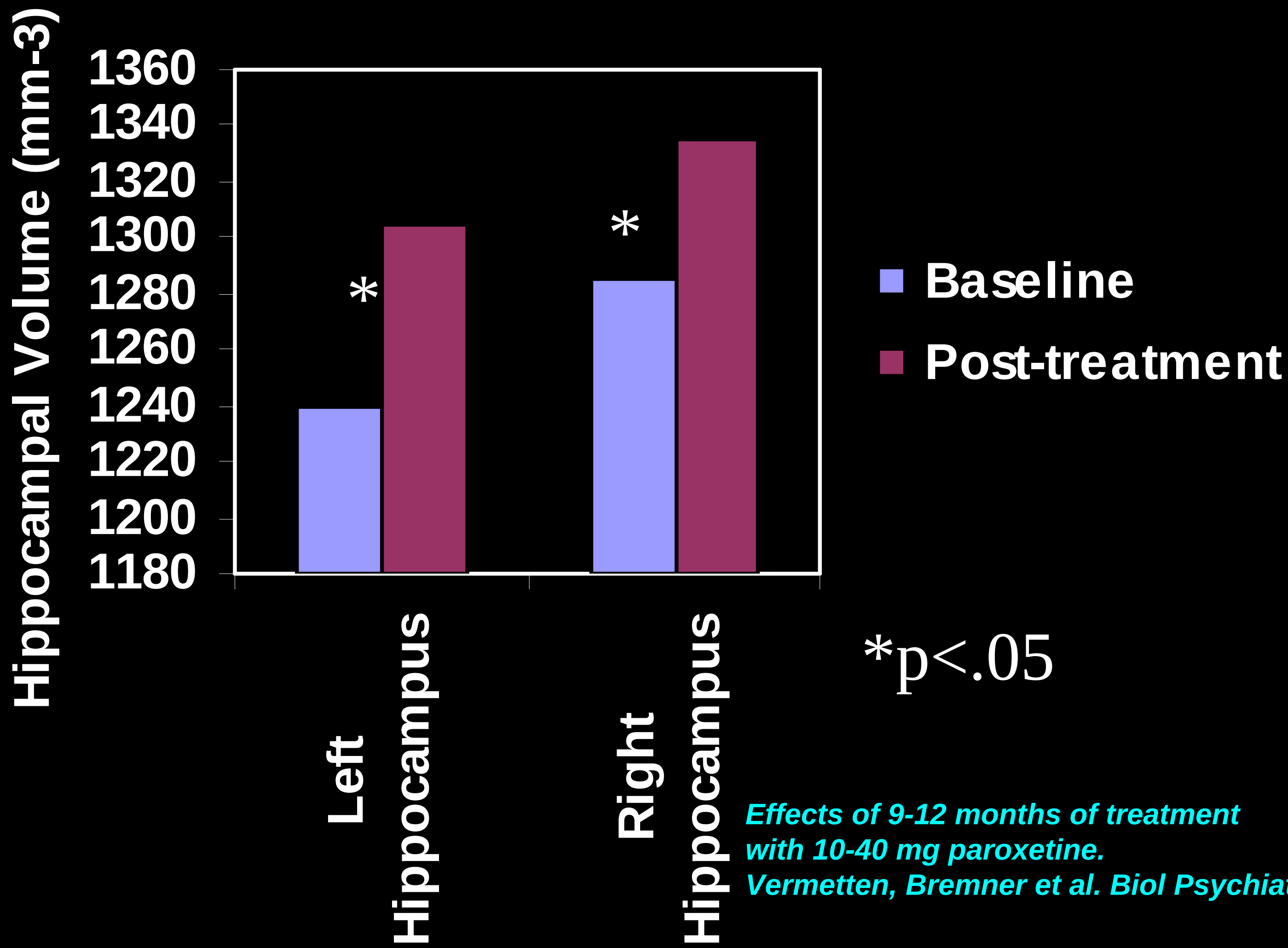

Normal
Stress
Antidepressants
↑ Glucocorticoids
↓ BDNF
↑ Serotonin and NE
↑ BDNF
↓ Glucocorticoids
Normal Survival and Growth
Atrophy/Death of Neurons
Increased Survival and Growth
Genetic Factors
Other neuronal insults:
♦ Hypoxia-Ischemia
♦ Hypoglycemia
♦ Neurotoxins
♦ Viruses
Modifed from Duman. Heninger, & Nestler, AGP 54(7):597-606, 1997

Effects of Paroxetine on Hippocampal-based Verbal Declarative Memory in PTSD



Effects of 9-12 months of treatment with 10-40 mg paroxetine, Vermetten et al Biol Psychiatry 2003

Increased Hippocampal Volume with Paxil in PTSD



Effects of 9-12 months of treatment with 10-40 mg paroxetine.
Vermetten, Bremner et al. Biol Psychiatry 2003.

Brain Circuits in Trauma Spectrum Disorders: Brain Volumes

	Hippo-campus	Amyg-Dala	mPFC/ AC/ Obf
PTSD	↓	NC	↓
Depression/ Abuse	↓	NC	↓
BPD	↓	↓	↓
DID	↓	↓	?

Brain Circuits in Trauma Spectrum Disorders: Brain Function

	Hippo-campus	Amyg-Dala	mPFC/ AC/ Obf
PTSD	↓	↑	↓
Depression/ Abuse	↓	↑	↓
BPD	↓	↑	↓
DID			

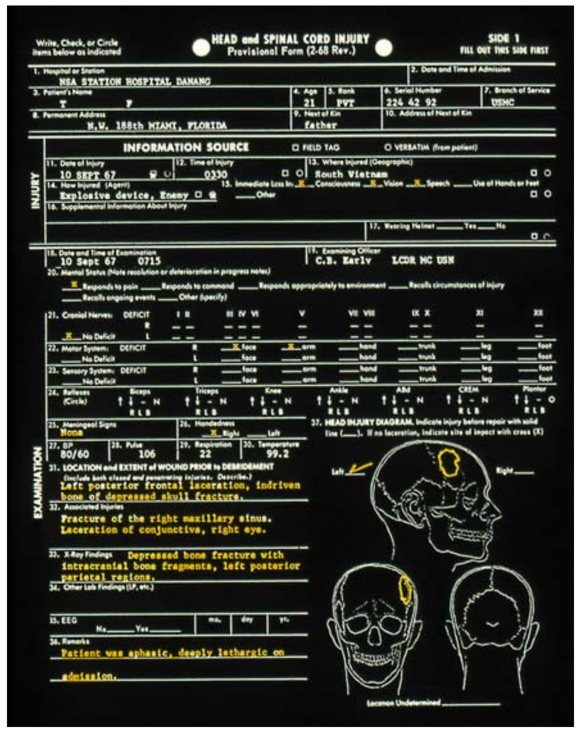
Conclusions

- Amygdala, hippocampus and prefrontal cortex mediate symptoms of PTSD and related trauma spectrum disorders (DID, BPD)
- Variations in interaction of stress with individual factors (genetics, etc) mediate differences in outcome
- Future research needed to assess similarities and differences in trauma spectrum disorders

Two Long Term Consequences of Combat-Related Penetrating Head Injuries:Exacerbated Decline and Post-Traumatic Stress Disorder

Jordan Grafman, Ph.D.

Chief, Cognitive Neuroscience Section
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Bethesda, Maryland



Write, Check, or Circle items below as indicated

HEAD and SPINAL CORD INJURY
Provisional Form (2-68 Rev.)

SIDE 1
FILL OUT THIS SIDE FIRST

1. Hospital or Station: NSA STATION HOSPITAL DANANG
2. Date and Time of Admission:
3. Patient's Name: T F
4. Age: 21
5. Rank: PVT
6. Serial Number: 224 42 92
7. Branch of Service: USMC
8. Permanent Address: N.W. 188th MIAMI, FLORIDA
9. Next of Kin: father
10. Address of Next of Kin:

INJURY

INFORMATION SOURCE ☐ FIELD TAG ○ VERBATIM (from patient)

11. Date of Injury: 10 SEPT 67
12. Time of Injury: 0330
13. Where Injured (Geographic): South Vietnam
14. How Injured (Agent): Explosive device, Enemy
15. Immediate Loss In: X Consciousness X Vision X Speech ___ Use of Hands or Feet ___ Other
16. Supplemental Information About Injury
17. Wearing Helmet ___ Yes ___ No

EXAMINATION

18. Date and Time of Examination: 10 Sept 67 0715
19. Examining Officer: C.B. Early LCDR MC USN
20. Mental Status (Note resolution or deterioration in progress notes): X Responds to pain ___ Responds to command ___ Responds appropriately to environment ___ Recalls circumstances of injury ___ Recalls ongoing events ___ Other (specify)
21. Cranial Nerves: DEFICIT R / L — I II, III IV VI, V, VII VIII, IX X, XI, XII; X No Deficit
22. Motor System: DEFICIT R: X face X arm ___ hand ___ trunk ___ leg ___ foot; L: ___ face ___ arm ___ hand ___ trunk ___ leg ___ foot; ___ No Deficit
23. Sensory System: DEFICIT R: ___ face ___ arm ___ hand ___ trunk ___ leg ___ foot; L: ___ face ___ arm ___ hand ___ trunk ___ leg ___ foot; ___ No Deficit
24. Reflexes (Circle): Biceps, Triceps, Knee, Ankle, ABd, CREM, Plantar — ↑ ↓ - N, R L B
25. Meningeal Signs: None
26. Handedness: X Right ___ Left
27. BP: 80/60
28. Pulse: 106
29. Respiration: 22
30. Temperature: 99.2
31. LOCATION and EXTENT of WOUND PRIOR to DEBRIDEMENT (Include both closed and penetrating injuries. Describe.): Left posterior frontal laceration, indriven bone of depressed skull fracture.
32. Associated Injuries: Fracture of the right maxillary sinus. Laceration of conjunctiva, right eye.
33. X-Ray Findings: Depressed bone fracture with intracranial bone fragments, left posterior parietal regions.
34. Other Lab Findings (LP, etc.)
35. EEG No ___ Yes ___ mo. day yr.
36. Remarks: Patient was aphasic, deeply lethargic on admission.
37. HEAD INJURY DIAGRAM. Indicate injury before repair with solid line (___). If no laceration, indicate site of impact with cross (X)

Left ___ Right ___

Location Undetermined ___

Acknowledgments: Dr. Andres Salazar, the following agencies: VA, DoD, NIH, and especially the Vietnam Veterans who have consistently volunteered to participate in our grueling research for no direct benefit in the hopes that others would be helped by their participation.

Outline

- **Background of the Vietnam Head Injury Study (VHIS)**

  Description of patients and limitations
  Advantages of studying brain-injured veterans
  Scientific hypotheses and clinical outcomes

- **VHIS Phase 3 (35-40 years postinjury): Consequence 1: Exacerbated Decline & Consequence 2: PTSD**

- **Summary & Discussion**

Description of patients and limitations

- 95%+ suffered PHI, generally between 18-25, all males, all reasonably healthy prior to PHI, majority caucasion
- Neurosurgeons in selected field hospitals completed a registry form (biases in completing form)
- Can only study those who agreed to come to WRAMC, NIH or NNMC
- Studies span from <5 years post-injury, 15 years post-injury, 35 years post-injury

Advantages of studying brain-injured veterans

- **Pre-injury intelligence estimate (AFQT) available [as is AGCT]**
- **All healthy prior to injury, similar education level, all young**
- **Post-injury follow-up (military & VA records) is relatively easy to obtain and there is a general willingness to volunteer for long-term studies in order to help future injured veterans**
- **Good test-retest reliability**
- **Can have direct impact on veteran health care**

Scientific hypotheses and clinical outcomes

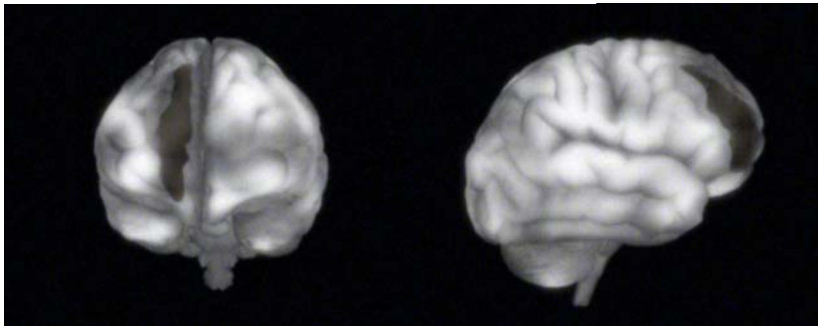
•**Military-related PHI can provide unique evidence about both short- and long-term neuronal plasticity and recovery of function/late-life decline.**

•**For example, studies can address the interaction between PHI, normal age-associated neuronal loss, and dementia (exacerbated decline).**

•**Military-related PHI can supplement civilian TBI research in determining the effect of HI on PTSD.**

•**For example, studies can address the role of certain brain structures in sustaining or reducing the effects of PTSD (amygdala, PFC, and hippocampus).**

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.



Example of CT scan findings in a VHIS patient.

Outline

- **Background of the Vietnam Head Injury Study (VHIS)**

  Description of patients and limitations
  Advantages of studying brain-injured veterans
  Scientific hypotheses and clinical outcomes

- **VHIS Phase 3 (35-40 years postinjury): Two Studies**

- **Summary & Discussion**

Phase III: Exacerbated Decline

Phase III: Post-Traumatic Stress Disorder

Manuscripts submitted

DEMOGRAPHIC, STRUCTURAL AND GENETIC PREDICTORS OF LATE COGNITIVE DECLINE FOLLOWING PENETRATING HEAD INJURY

Vanessa Raymont[1&2], Amanda Greathouse[1&2], Katherine Reding[1&2], Robert Lipsky[3], Andres Salazar[2], and Jordan Grafman[2*]

1 Vietnam Head Injury Study, Henry M. Jackson Foundation, National Naval Medical Center, Bethesda, Maryland, 20889, USA.
2 Cognitive Neuroscience Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, 20892, USA.
3 Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland, 20892, USA.

Acknowledgements

VR, AG and KR are supported by a project grant from the United States Army Medical Research and Material Command and administered by the Henry M. Jackson Foundation (ŅVietnam Head Injury Study Phase III: A 30 Year Post-Injury Follow-Up Study,Ó: Grant number: DAMD17-01-1-0675). JG is supported by the National Institute of Neurological Disorders and Stroke intramural research program.

1) **Please send reprint requests and correspondence to:**

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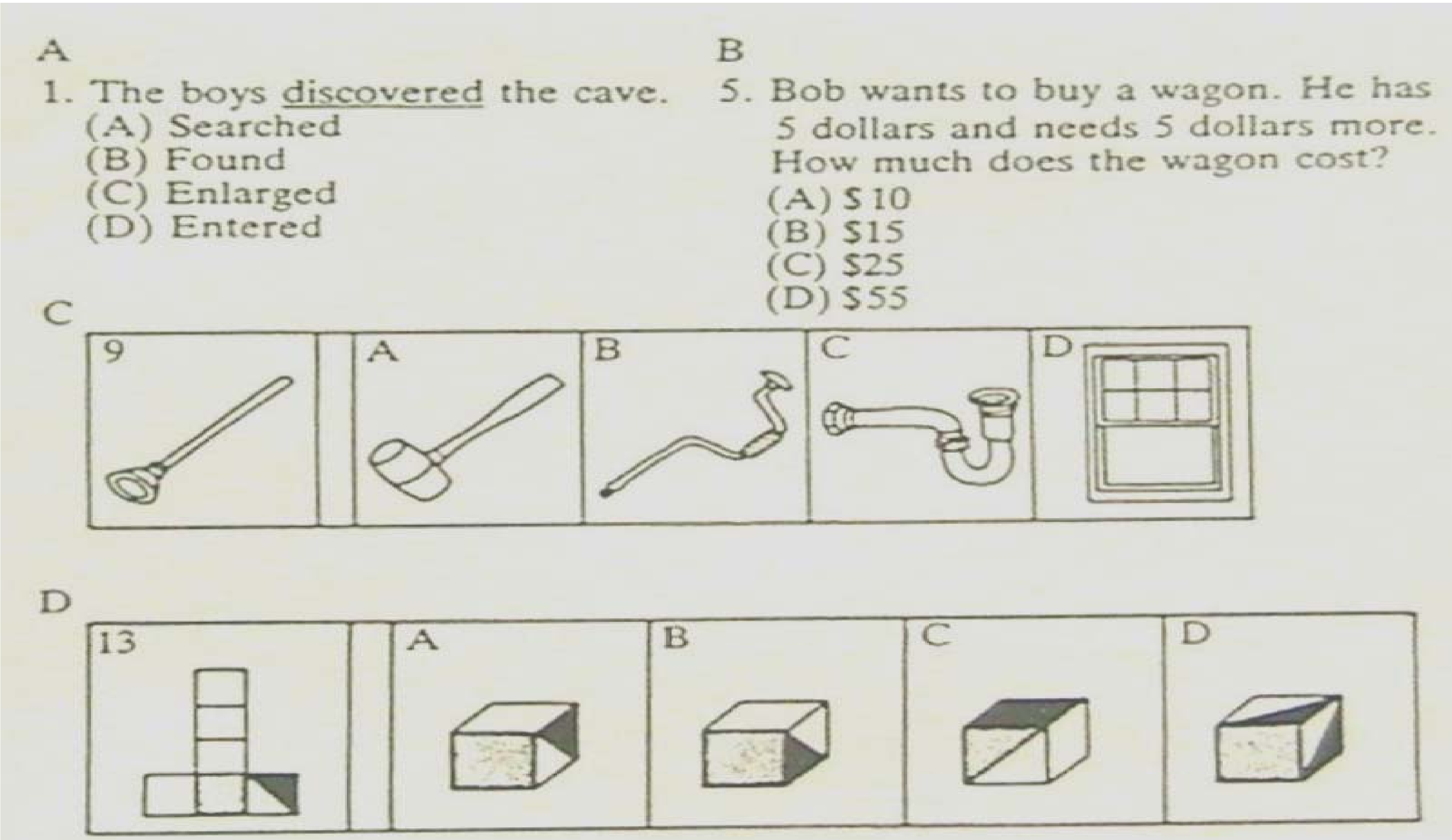
The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.

Table 1 Š Comparison of head-injured and control subjects at P3

		Mean	Std. Deviation	p
Age at testing	Control N=55	59.15	3.873	
	Head-injured N=199	58.11	2.940	
	Total	58.31	3.155	0.061
Years of education	Control	14.16	2.398	
	Head-injured	14.20	2.270	
	Total	14.19	2.283	0.922
Preinjury intelligence	Control	65.40	22.91	
	Head-injured	59.91	25.54	
	Total	6078	25.18	0.238

Figure 1 Š Sample of questions AFQT



Mini-Mental State Scores

Controls	Median Score=30
PHI	Median Score=29 4.5% had a score <24 with greater decline from preinjury to P3 but also had lower preinjury AFQT score

16.57% of PHI had family hx of dementia, no differences with other PHI pts based on MMSE, atrophy, or decline in AFQT score.

Bias: P3 compared to P2 attenders (PHI) tended to have higher pre-injury AFQT scores and more total years of education.

Correlation with IQ scores: AFQT total score is highly correlated with the WAIS III Full-Scale IQ score for both PHI (r=.82) and controls (r=.85).

RESULTS

Controls: P2--->P3 median decline of 4.0 points

PHI: P2--->P3 median decline 7.0 points

Marginal difference (p=.06)

Table 1 - Mean changes in AFQT scores from preinjury to P3 based on preinjury AFQT grouping in head-injured subjects only

Preinjury deciles	N	Mean change	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
10	3	6.00	4.36	2.52	-4.83	16.83	1.00	9.00
2	11	7.00	11.33	3.42	-.613	14.61	-7.00	26.00
3	12	1.50	11.69	3.37	-5.93	8.93	-11.00	29.00
4	16	.75	17.00	4.25	-8.31	9.81	-20.00	26.00
5	16	-9.31	14.53	3.63	-17.06	-1.57	-33.00	23.00
6	19	-3.53	24.52	5.63	-15.34	8.29	-47.00	27.00
7	20	-13.55	20.96	4.69	-23.36	-3.74	-53.00	15.00
8	27	-13.93	20.23	3.89	-21.93	-5.92	-57.00	15.00
9	39	-16.03	18.33	2.94	-21.97	-10.08	-73.00	8.00
10	19	-14.12	12.95	2.97	-20.35	-7.86	-44.00	5.00
Total	182	-8.96	19.14	1.42	-11.76	-6.16	-73.00	29.00

AFQT Decline from P2 --------> P3

Predictor	% Variance Accounted for
Preinjury AFQT	**12.7%**
Caudate Involvement	**14.7%**
Left Parietal Involvement	**4.2%**
Hippocampal Involvement	**4%**
Right Amygdala Involvement	**2%**
Right Frontal Involvement	**1.8%**
Corpus Callosum Atrophy	**3.6%**

Genetic Markers (similar incidence in our sample)

Time Period	Significant Predictor(s)
Preinjury AFQT	Grin 2C, GAD2, DBH444, Grin2B (sig) with COMT 2255423 and APOe4 allele (marginal) ~ 18% of variation
Preinjury-->Phase 2	2 GAD markers and COMT predicted better recovery of AFQT Score
Preinjury/Phase 2 -->Phase 3	GRIN 2A predicted greater decline

Focal brain damage protects against post-traumatic stress disorder in combat veterans

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3. Medical Numerics, Germantown, MD, USA

[*] To whom correspondence should be addressed. E-mail: grafmanj@ninds.nih.gov

please don’t quote without authors’ permission

Abstract

Post-traumatic Stress Disorder (PTSD) is an often debilitating psychopathology characterized by recurrent distressing memories of traumatic events. Neuroimaging data associate PTSD with abnormalities in ventromedial prefrontal cortex (vmPFC), amygdala, and hippocampus, but the direction of causality is unclear. To investigate the causal relationship of neuropathology and PTSD symptomology, we used a unique sample of Vietnam War veterans who suffered brain injury and emotionally traumatic events to identify brain areas where damage affected the subsequent development of PTSD.

Supporting Tables

Group	n	Age	Sex (% male)	Race (% Cauc)	Education (years)	MMSE
Amygdala	15	57.8 (2.3)	100	93	14.6 (3.2)	27.8 (2.0)
vmPFC	40	58.0 (3.1)	100	92	14.1 (6.7)	27.9 (2.9)
Non-vmPFC/non-amygdala	132	58.5 (3.2)	100	89	15.0 (2.5)	28.6 (1.7)
No brain damage	52	59.0 (2.5)	100	87	15.2 (2.5)	29.1 (1.3)

Table S1. Participant data at time of Phase 3 clinical evaluation. For ŅAge,Ó ŅEducation,Óand ŅMMSE,Ómean values are given with standard deviations in parentheses. ŅAgeÓrefers to years at the time of SCID administration. ŅSex (% male)Óis the percentage of male subjects. ŅRace (% Cauc)Óis the percentage of Caucasian subjects. ŅMMSEÓis the Mini Mental State Examination (*8*), a test of basic cognitive function. Any score over 25 (out of 30) is effectively normal.

Group	Age in Vietnam	% Drafted	AFQT (%ile)	AFQT Change	Combat Exposure	Combat Exposure (% high)
Amygdala	20.4 (2.2)	50	65.6 (28.1)	-15.2 (23.9)	3.9 (1.6)	64
vmPFC	20.3 (3.1)	36	55.0 (22.6)	-9.7 (17.9)	3.2 (0.8)	43
Non-vmPFC/ non-amygdala	20.6 (2.9)	31	61.3 (25.9)	-8.2 (19.0)	3.3 (1.1)	58
No brain damage	20.6 (3.1)	52	65.4 (22.9)	3.9 (14.5)	2.6 (1.2)	33

Group	Reexperience	Avoidance/Numbing	Hyperarousal
Amygdala	1.40	1.07	1.13
vmPFC	2.08	1.87	1.92
Non-vmPFC/Non-amygdala	2.40	2.29	2.16
No brain damage	2.63	2.77	2.31

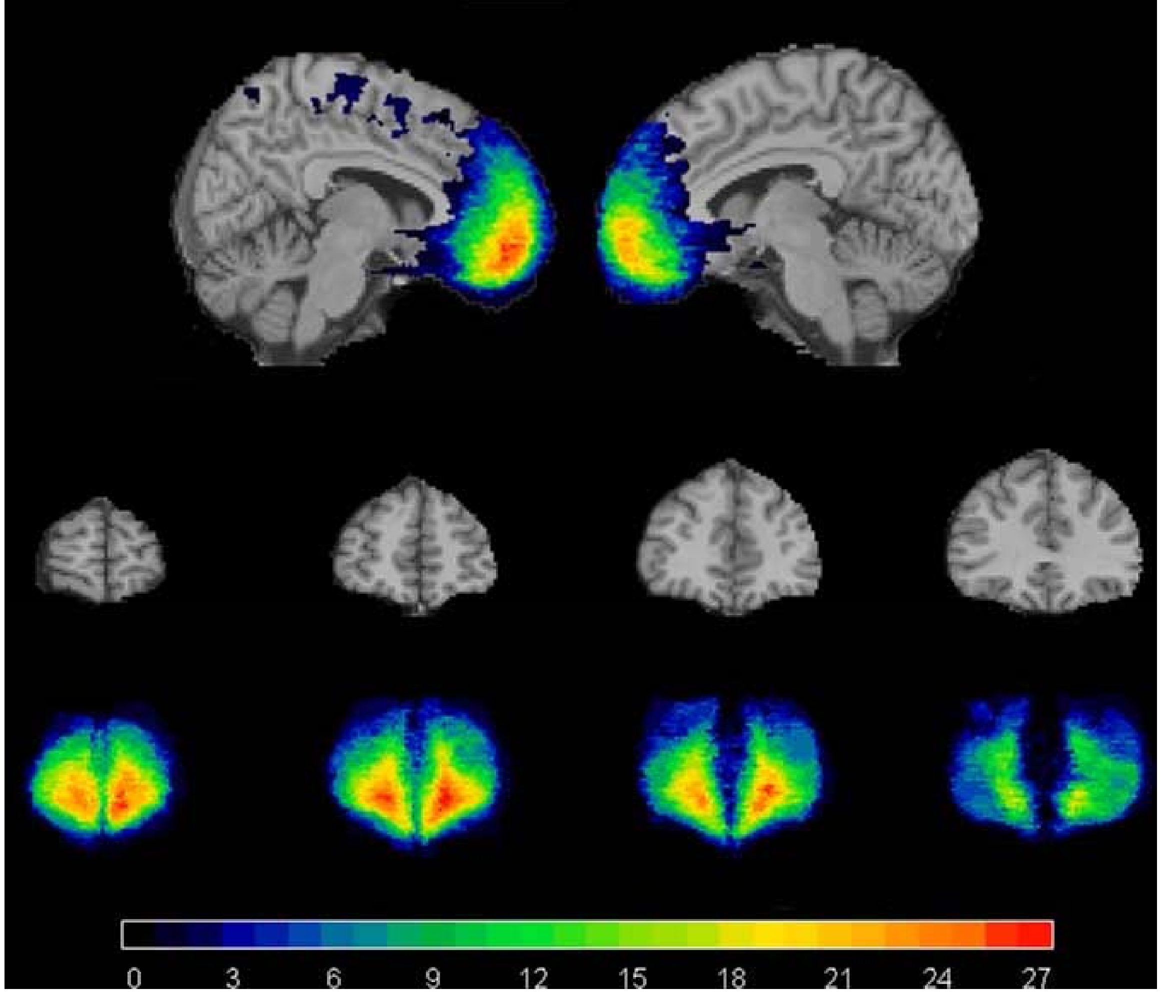


Fig 2. vmPFC group lesion overlap map. The color indicates the number of veterans in the vmPFC group (n=40) with damage to a given voxel. The greatest lesion overlap (red) occurs in the anterior vmPFC bilaterally. Top row: Sagittal views of the vmPFC group lesion overlap. The left hemisphere (x=-8) is on the left; the right hemisphere (x=6) is on the right. Middle row: Coronal views of a healthy adult brain. Slices are arranged with the anterior-most slice on the left (y=66; y=56; y=46; y=36; respectively). Bottom row: Coronal views of the vmPFC group lesion overlap, corresponding to the slices in the middle row. Of the forty vmPFC patients, fourteen had bilateral vmPFC lesions, fifteen had exclusively or predominantly left vmPFC lesions, and eleven had exclusively or predominantly right vmPFC lesions. Of the seven vmPFC patients who developed PTSD, two had bilateral vmPFC lesions, two had exclusively or predominantly left vmPFC lesions, and three had exclusively or predominantly right vmPFC lesions.

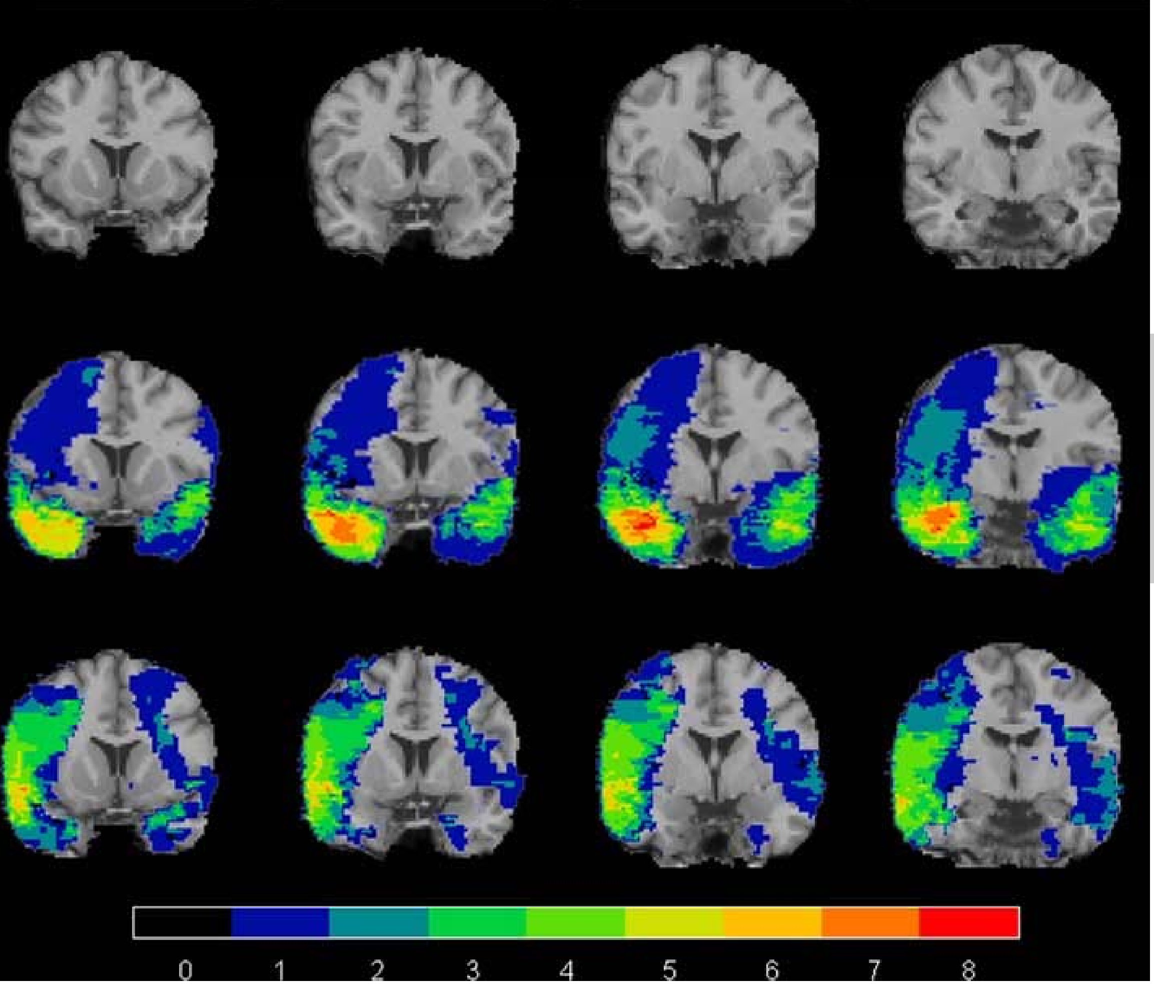


Fig 3. Lesion overlap maps for the amygdala and amygdala comparison groups. The color indicates the number of veterans with damage to a given voxel. Top row: Coronal views of a healthy adult brain. Slices are arranged with the anterior-most slice on the left (y=14; y=8; y=2; y=-4; respectively). Middle row: Coronal views of the amygdala group lesion overlap. Bottom row: Coronal views of the amygdala comparison group lesion overlap. Slices in the middle and bottom rows correspond to the top row. The overlap maps are similar, except for the medial anterior temporal area containing the amygdala, which is damaged in the amygdala group but intact in the amygdala comparison group. Of the fifteen amygdala patients, seven had damage to the left amygdala and eight had damage to the right amygdala.

Memory Test scores of Veterans w/o PTSD are within normal limits

WMS-III Test	Score
General Memory Index	97.2 (17.3)
Auditory Delayed	100.2 (16.4)
Visual Delayed	94.6 (19.0)
Verbal Paired-Associates	16.5 (9.3)

Tables

Table 1. PTSD prevalence. Veterans are grouped based on the presence/location of brain damage. A chi-square frequency analysis of the three groups of brain-injured veterans indicates a significant effect of lesion location on PTSD prevalence (χ^2 =14.7; p=.0006). p-values for individual pairwise comparisons are given in the text and summarized in Table S3. Chi-square tests are used for pairwise comparisons if there are at least five individuals with (or without) PTSD diagnosis in both groups; if not, FisherÕs exact test is used.

Brain damage	PTSD prevalence
Amygdala	0%
vmPFC	18%
non-vmPFC/non-Amygdala	40%
No brain damage	48%

Pairwisecomparison	p-value
Amygdala vs. No brain damage	**0.0005**
Amygdala vs. Non-vmPFC/non-amygdala	**0.001**
vmPFC vs. No brain damage	**0.002**
vmPFC vs. Non-vmPFC/non-amygdala	**0.009**
Amygdala vs. Non-amygdala temporal	**0.01**
vmPFC vs. Amygdala	0.09
Non-amygdala temporal vs. No brain damage	0.17
Non-vmPFC/non-amygdala vs. No brain damage	0.31
Non-amygdala temporal vs. Non-vmPFC/non-amygdala	0.45

Outline

- **Background of the Vietnam Head Injury Study (VHIS)**

  Description of patients and limitations
  Advantages of studying brain-injured veterans
  Scientific hypotheses and clinical outcomes

- **VHIS Phase 3 (35-40 years postinjury): Selected Analyses**

- **Summary & Discussion**

Summary

- The effects of lesions are persistent with most causing impairments but occasionally they can be considered protective (PTSD).
- Evidence for late life exacerbated decline is accumulating.
- Excellent patient group for answering some basic questions in cognitive neuroscience.
- The act of answering those questions can lead to changes in how brain-injured patients are cared for.

Discussion

- Continued research on simple long-term outcomes (e.g., working or not).
- Continued research on specific social cognitive outcomes (e.g., obeying social rules concerned with politeness) that help predict simple outcomes.
- Continued research on savings to society (health care and other costs) by studying and treating this pt population.
- Continued study of neuroplasticity & aging effects (recovery of function, exacerbated decline, incidence of early-onset dementias) brain-injured Vets (female military HI).
- Similar studies of pure blast injuries.

Disruptive Innovation in Health Information Technology: The Role of "Search"

Michael L. Cowan MD,
Chief Medical Officer,
BearingPoint, Inc.

Innovation: Disruption Executive Summary

Healthcare Industry IT Issues

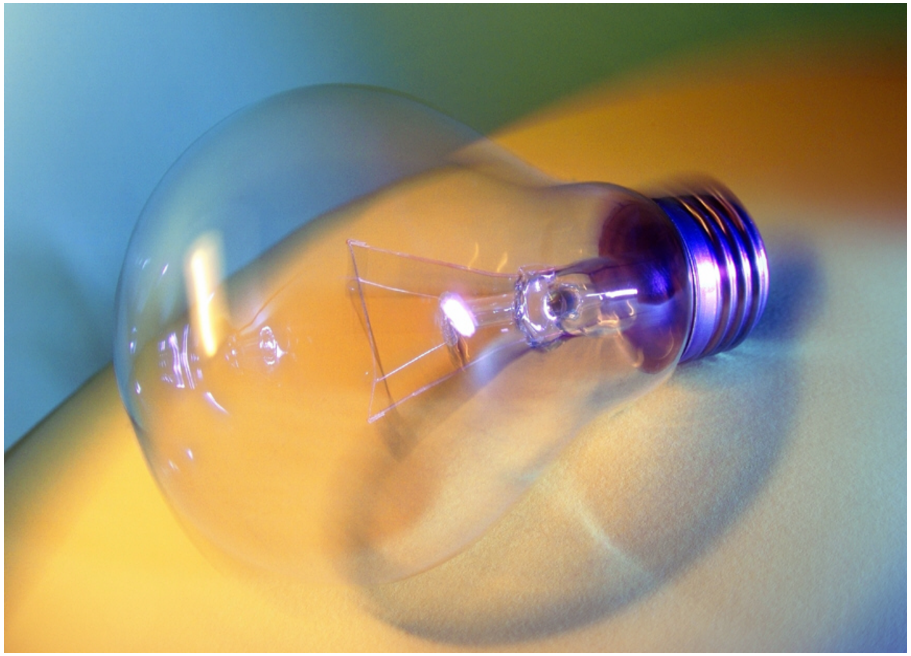
- Cost, Quality & Access

Health Information Technology

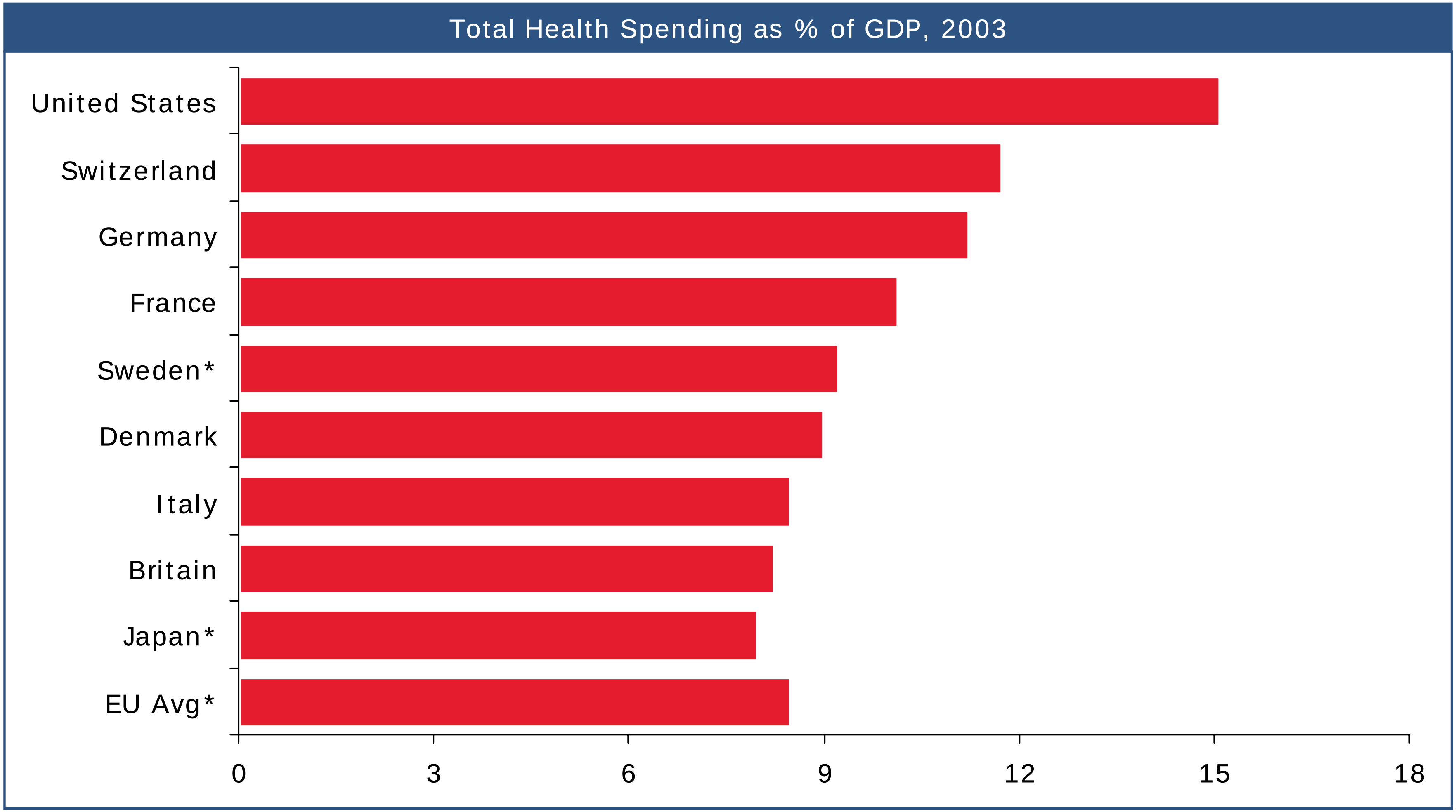
- Age of Software

Potential for Disruption

- Age of Networks

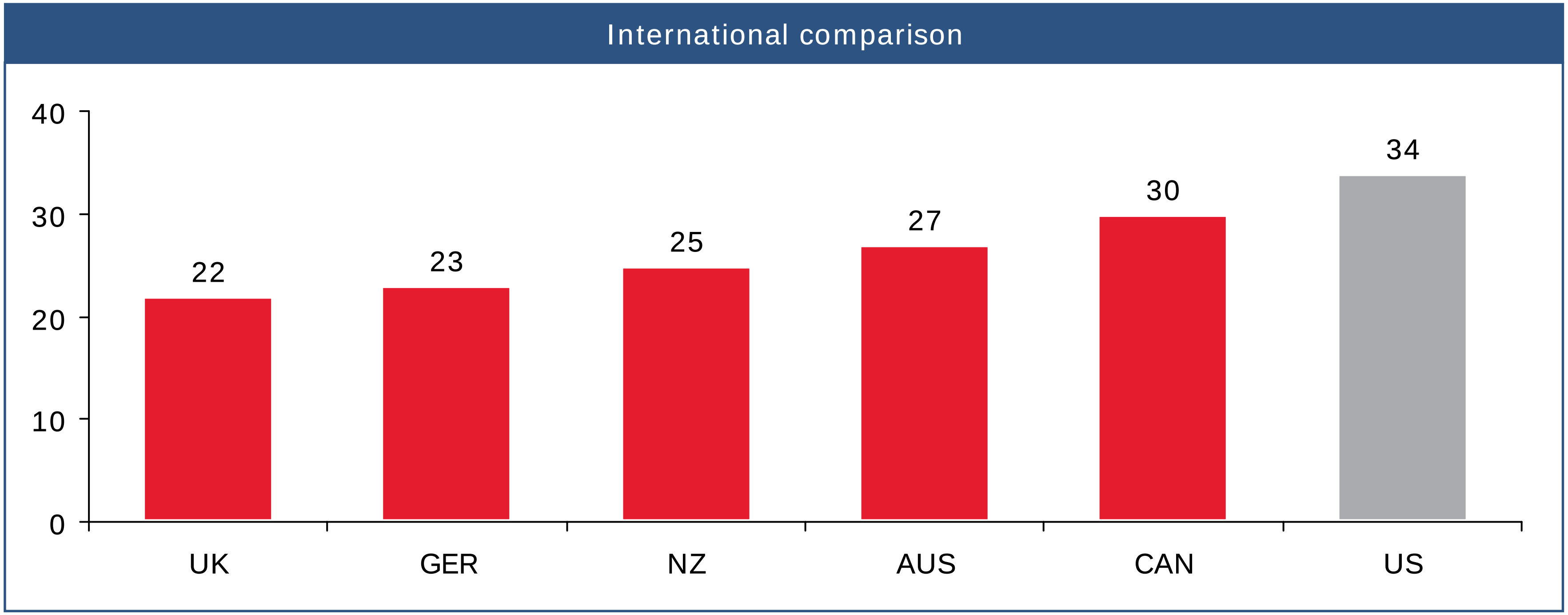


U.S. Healthcare Spending



Medical, Medication and Lab Errors

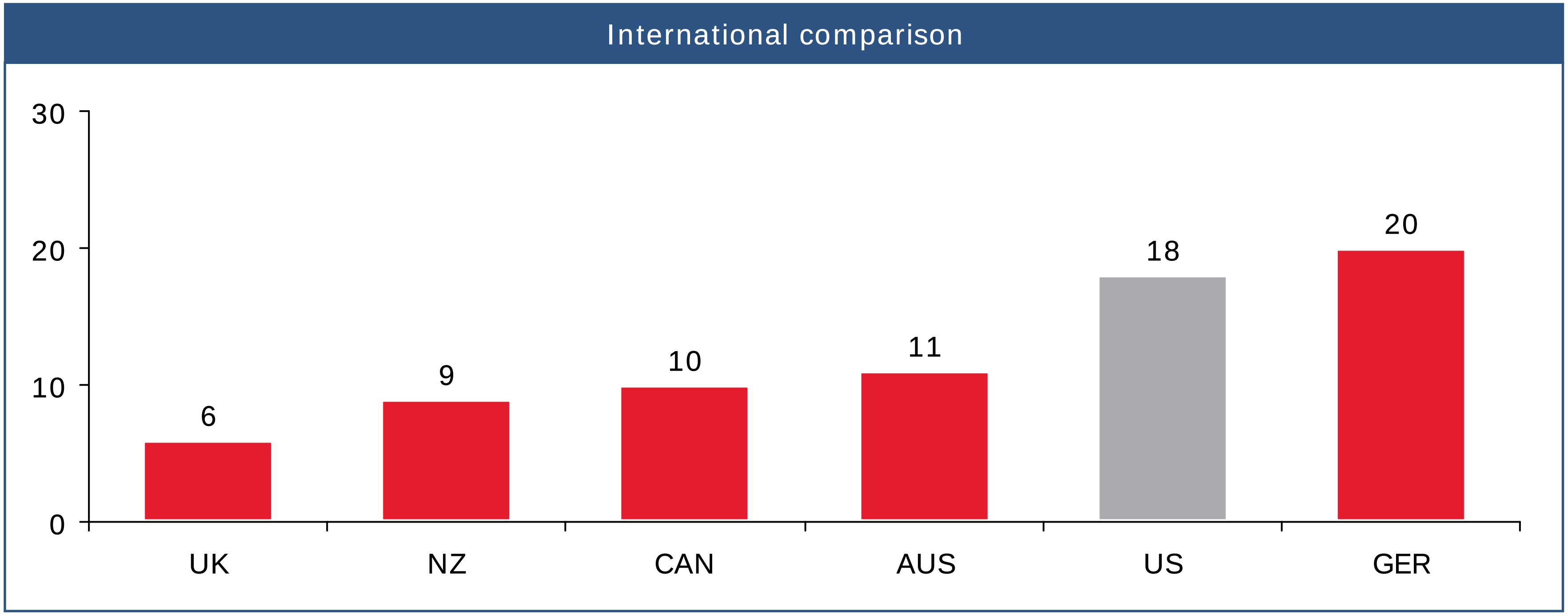
Percent reporting medical mistake, medication error, or lab error in past two years



UK=United Kingdom; GER=Germany; NZ=New Zealand; AUS=Australia; CAN=Canada; US=United States.
Data: Analysis of 2005 Commonwealth Fund International Health Policy Survey of Sicker Adults; Schoen et al. 2005a.

Source: Commonwealth Fund National Scorecard on U.S. Health System Performance, 2006

Duplicate Medical Tests, Among Sicker Adults, 2005

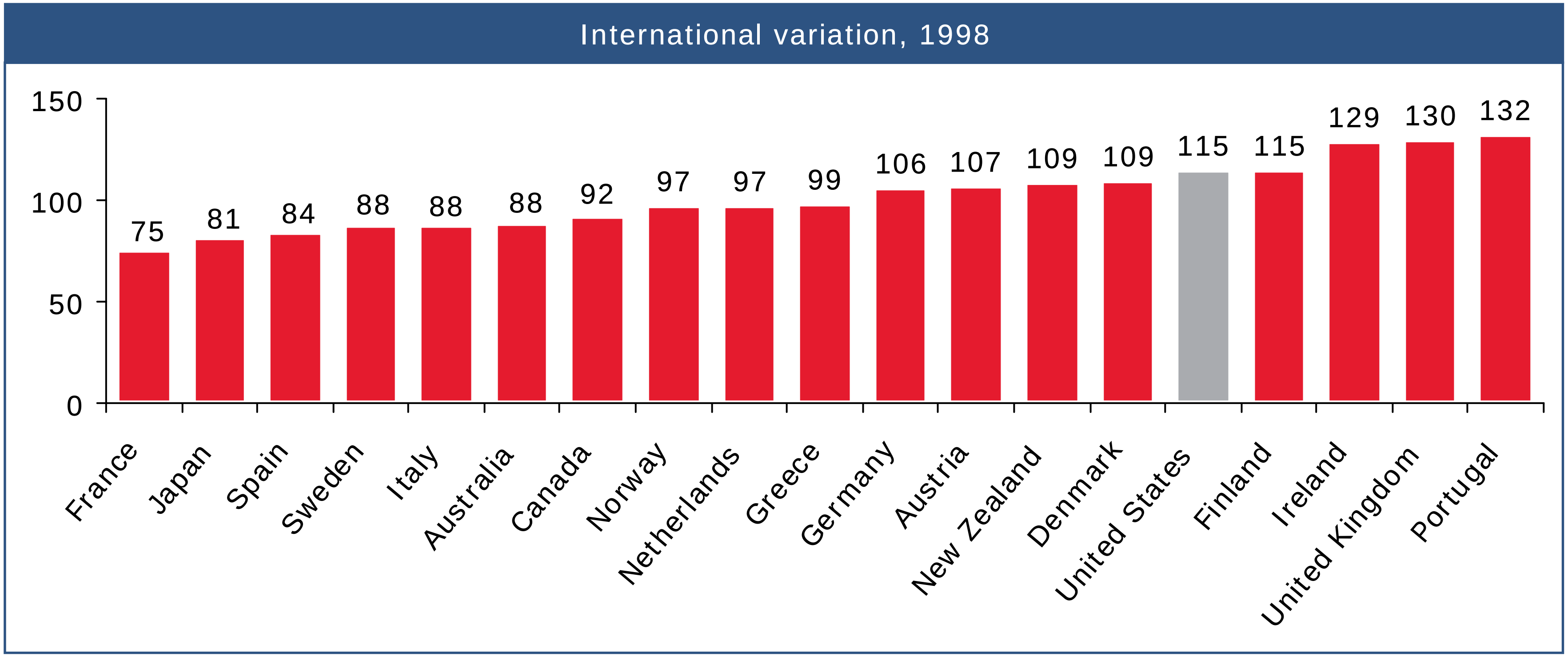


UK=United Kingdom; NZ=New Zealand; CAN=Canada; AUS=Australia; US=United States; GER=Germany.
Data: Analysis of 2005 Commonwealth Fund International Health Policy Survey of Sicker Adults; Schoen et al. 2005a.

Source: Commonwealth Fund National Scorecard on U.S. Health System Performance, 2006

Mortality Amenable to Health Care

Deaths per 100,000 population*



* Age-standardized death rates, ages 0–74; includes ischemic heart disease. World Health Organization, WHO mortality database (Nolte and McKee 2003);

Source: Commonwealth Fund National Scorecard on U.S. Health System Performance, 2006

Consumer Views of U.S. Healthcare

20% Satisfied with the Cost

- Average cost of employer sponsored insurance: $11,765
- Employee contribution $3,226

44% Satisfied with the Quality

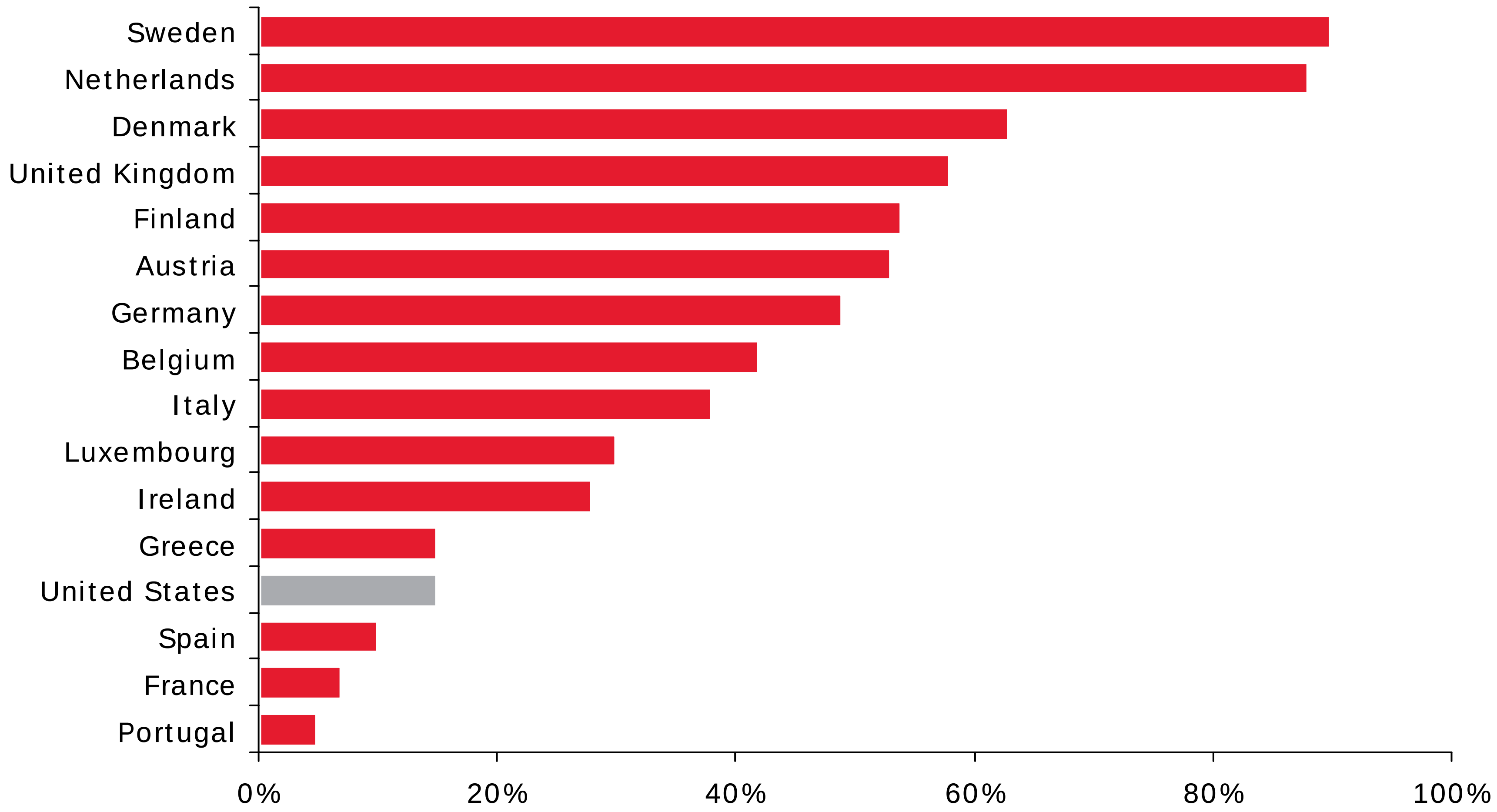
- 90% satisfied with own providers

Survey by USA TODAY, ABC News, and Kaiser Family Foundation, September 2006

Current Status: Importance of Information Technology – Cost & Quality

"We have repeatedly performed the definitive experiment and conclusively proven that paper based Health Records cannot support the complex information requirements of Modern Healthcare."

Current Status: HIT in U.S. Health Care

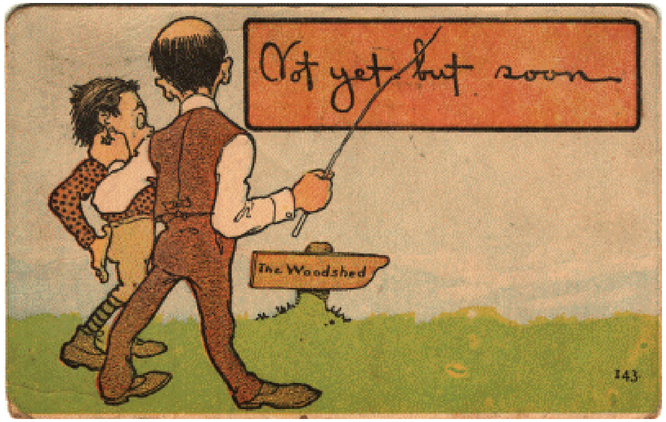


Source: Laura Adams, President and CEO, Rhode Island Quality Institute

Disruptive Era "A TRIP TO THE WOODSHED"

April 2004: Bush promised EHRs for all Americans in 10 years

- Established ONC HIT
  - No comparable office elsewhere
- Resulting Acronym Blizzard
  - NHIN
  - RHIOs
  - HIE
  - EHR
  - PHR



3 Years Later: Progress Has Been Slow

EHR usage study shows slow progress toward Bush's 2014 goal

Healthcare IT News

By Diana Manos, Senior Editor

10/11/06

- WASHINGTON – Findings released Wednesday from a first-ever, comprehensive study on the use of electronic health records in the United States revealed that 24.9 percent of physicians use some form of loosely defined EHRs, although fewer than 10 percent employ what researchers define as "a system most likely to benefit patient care."

- The 81-page report, Health Information Technology in the United States: The Information Base for Progress, also showed that only 5 percent of hospitals use computerized physician order entry (CPOE) systems, an indicator of EHR adoption in the in-patient setting.

The Myths and Realities of RHIOs

BearingPoint.

Reality: To date, there is **little evidence** that efforts have been able **to demonstrate ongoing sustainability**. In fact, FCG has found only two RHIOs that even claim to have a sustainable business model. One of the biggest problems is that while providers typically pay for the technology, the majority of benefits associated with health information exchange accrue to consumers, health plans, or employers. Without the participation and cooperation of all stakeholders (especially those who actually reap the benefits), any business model quickly falls apart.

From: FCG Executive Series

Inducing Change: The Case for Disruption

"We can't solve problems by using the same kind of thinking we used when we created them."

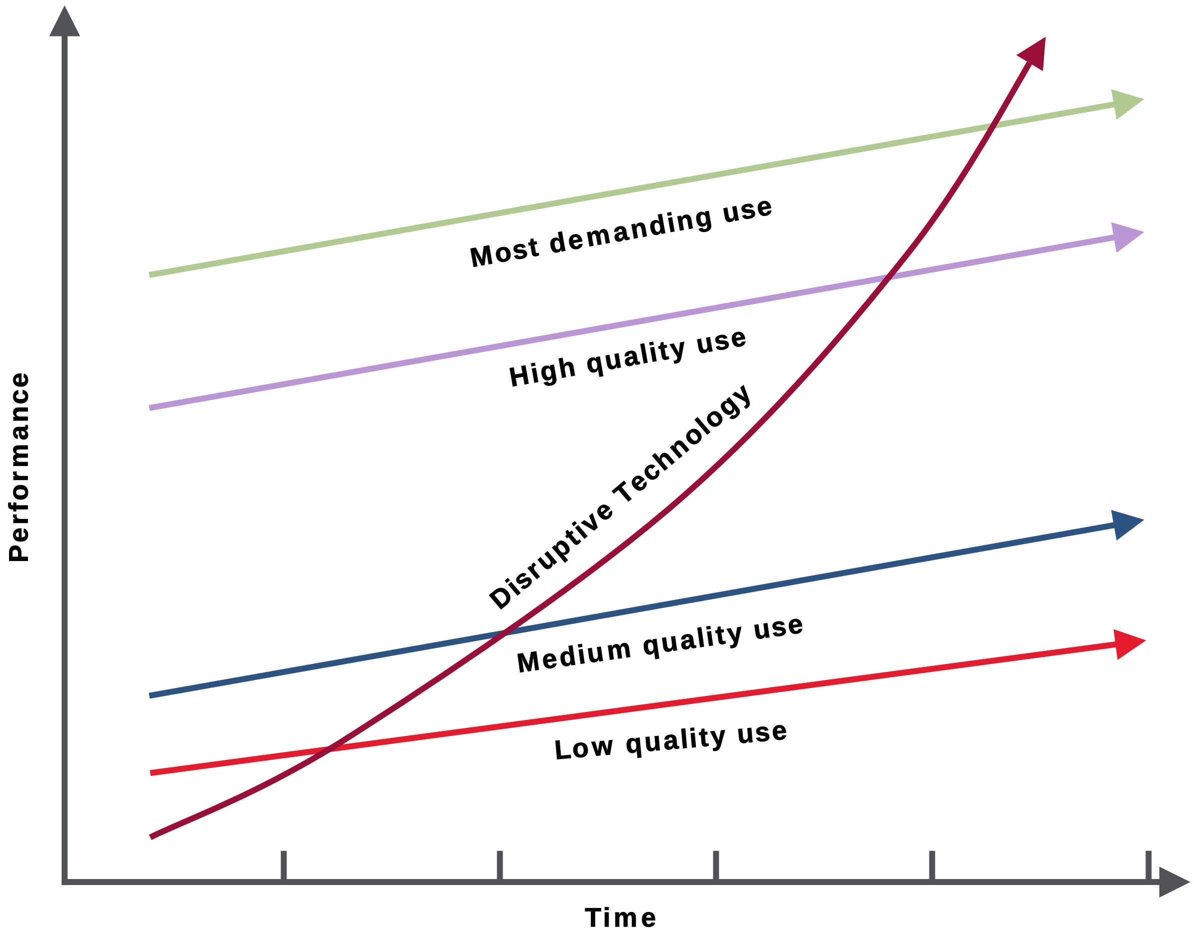
– Albert Einstein

Another Alternative: Disruptive Innovation

Disruption: a technological innovation, product, or service that eventually overturns the existing dominant technology or product in the market.

– Wikipedia

Natural History of Disruptive Innovation



Examples of Disruptive Innovations

Healthcare

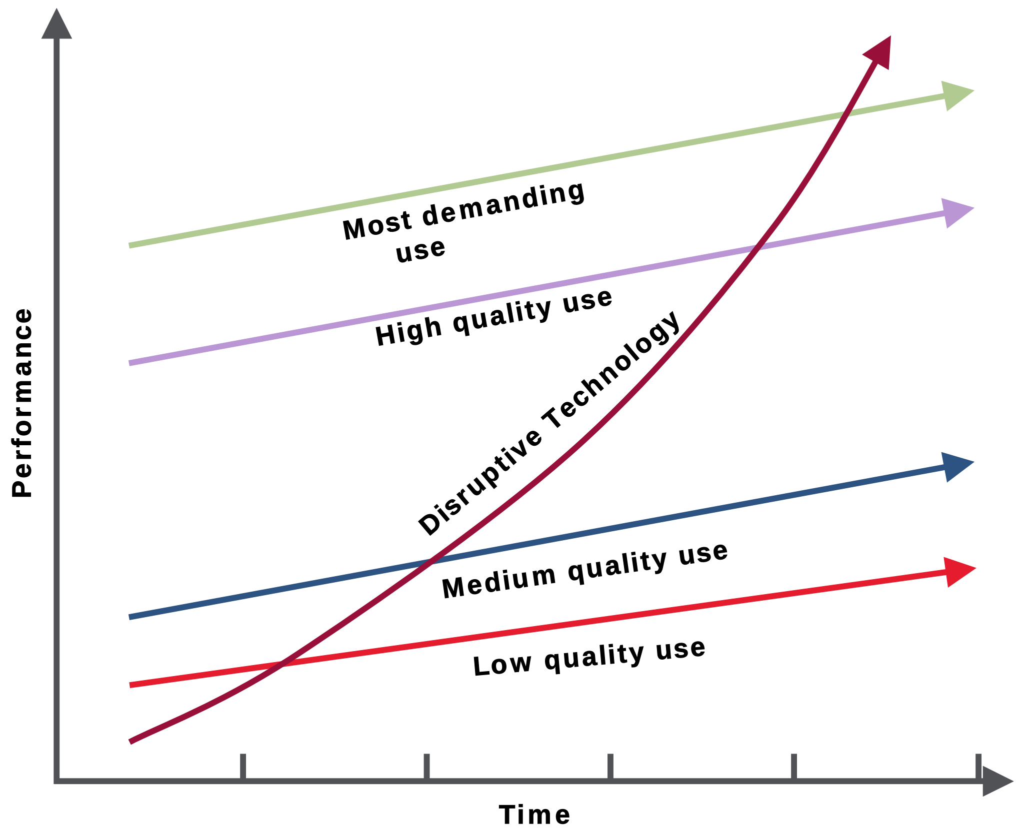
- Pregnancy Testing
- Nurse Practitioners

Technology

- Desktop/GUI
- Internet
- Digital Cameras
- E-Mail
- Search Engines

Others

- Toyotas
- IEDs and Suicide Bombers



Characteristics of Industries Ripe for Disruption

Industry Exceeds Requirements (Overshoot)

- Complexity and/or expense exceeds user needs

Industry Fails to Meet Minimum Requirements (Undershoot)

- Cost & Quality & Convenience

Asymmetries and Non-consumers (Dropouts)

- Potential Users Opt-out
- Variable Value

Is Healthcare Industry Ripe for Disruption?

Healthcare Overshoots: Industry Focus on high-end complex interventions

- Expensive Infrastructure

Healthcare also Undershoots: Difficult Navigation for Routine Care

- Earache

Asymmetries and Non-consumers

- 43 million uninsured
- $100B expenditures on alternative medicine

Health Information Technology Industry: "In Desperate Need of Disruption"

HIT Overshoots: Complexity

- Semantic Integration of Proprietary Systems and Data
- Complex HIT Systems on Unprecedented Scale

HIT also Undershoots the end-user

- EHR
  - Productivity and training costs
  - Changes in business and practice procedures

Non-Consumers Opt Out

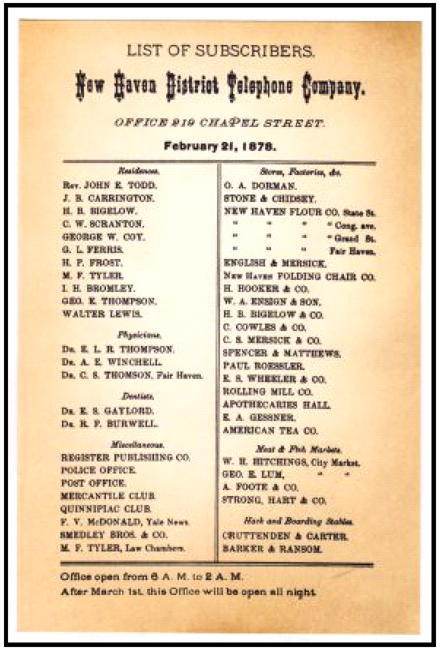
- Hospital CPOE use ~27%
- Small group and solo office practice EMR ~25%
  - 75% don't use EMR and have no plans to ever do so...

Organizing Principles: Telephone Directories

BearingPoint.

First Telephone Book

Alexander Graham Bell was granted a patent on his telephone in 1876. He demonstrated it to visitors to the Philadelphia Centennial E
same year. In early 1878, he installed the first telephone exchange, in New Haven, Connecticut. The first telephone "book" - actually
cm. x 21 cm. sheet - was issued in New Haven in 1878. Below is a 1978 facsimile of that sheet. To the right is the same text, suitable
searching.



LIST OF SUBSCRIBERS.

New Haven District Telephone Company.

OFFICE 219 CHAPEL STREET.

February 21, 1878.

Residences.	*Stores, Factories, &c.*
Rev. JOHN E. TODD.	O. A. DORMAN.
J. B. CARRINGTON.	STONE & CHIDSEY.
H. B. BIGELOW.	NEW HAVEN FLOUR CO. State St.
C. W. SCRANTON.	" " " " Cong. ave.
GEORGE W. COY.	" " " " Grand St.
G. L. FERRIS.	" " " Fair Haven.
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M. F. TYLER.	New Haven FOLDING CHAIR CO.
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WALTER LEWIS.	H. B. BIGELOW & CO.
	C. COWLES & CO.
Physicians.	C. S. MERSICK & CO.
Dr. E. L. R. THOMPSON.	SPENCER & MATTHEWS.
Dr. A. E. WINCHELL.	PAUL ROESSLER.
Dr. C. S. THOMSON, Fair Haven.	E. S. WHEELER & CO.
	ROLLING MILL CO.
Dentists.	APOTHECARIES HALL.
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REGISTER PUBLISHING CO.	W. H. HITCHINGS, City Market.
POLICE OFFICE.	GEO. E. LUM, " "
POST OFFICE.	A. FOOTE & CO.
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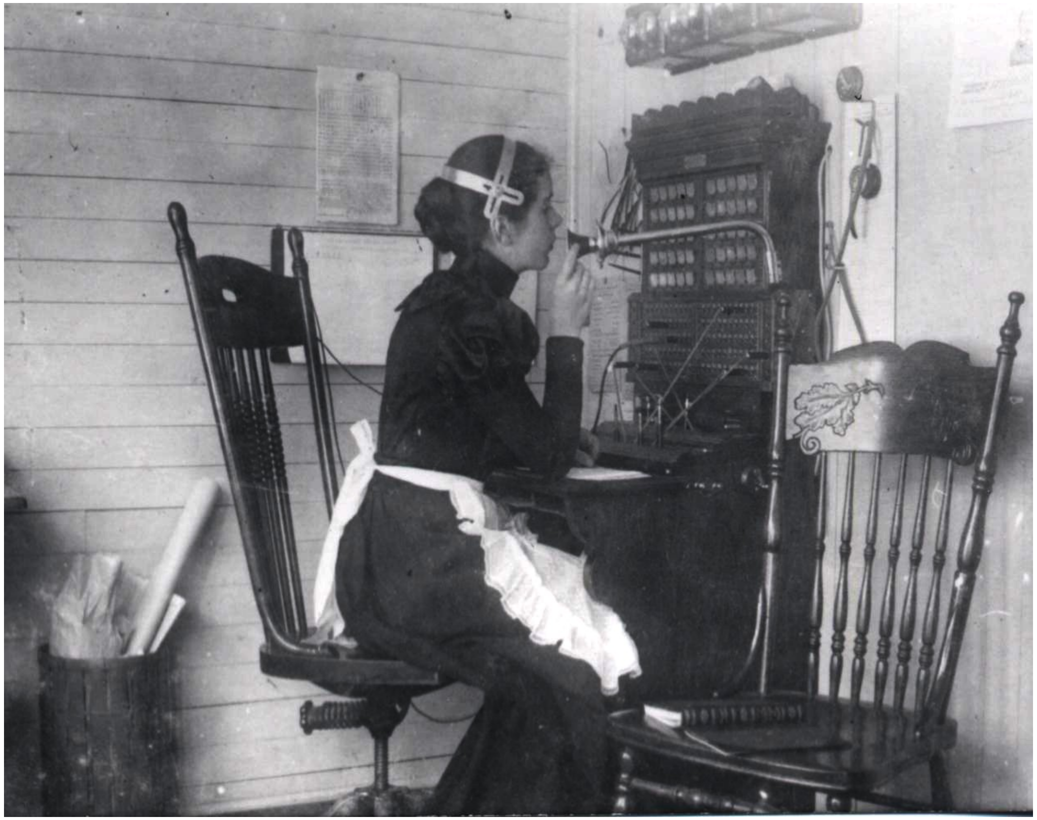
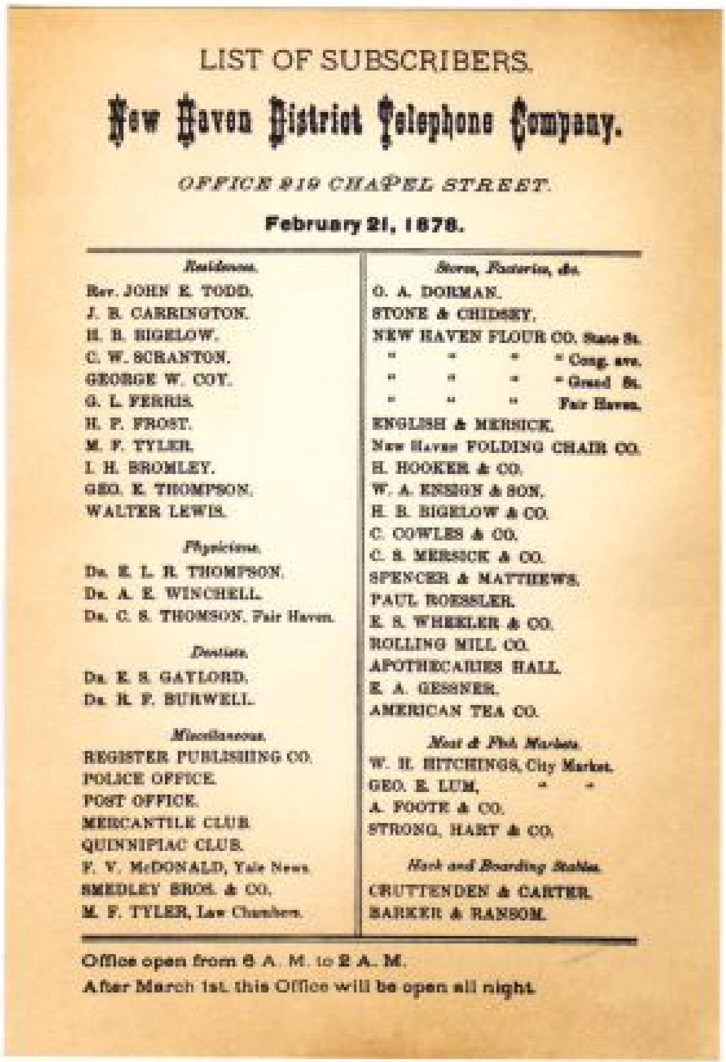
Information Management Organizing Principle:
The Lesson of Telephone Books

Search Engine

- "Louise v1.2"



Telephone Books



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A. FOOTE & CO.
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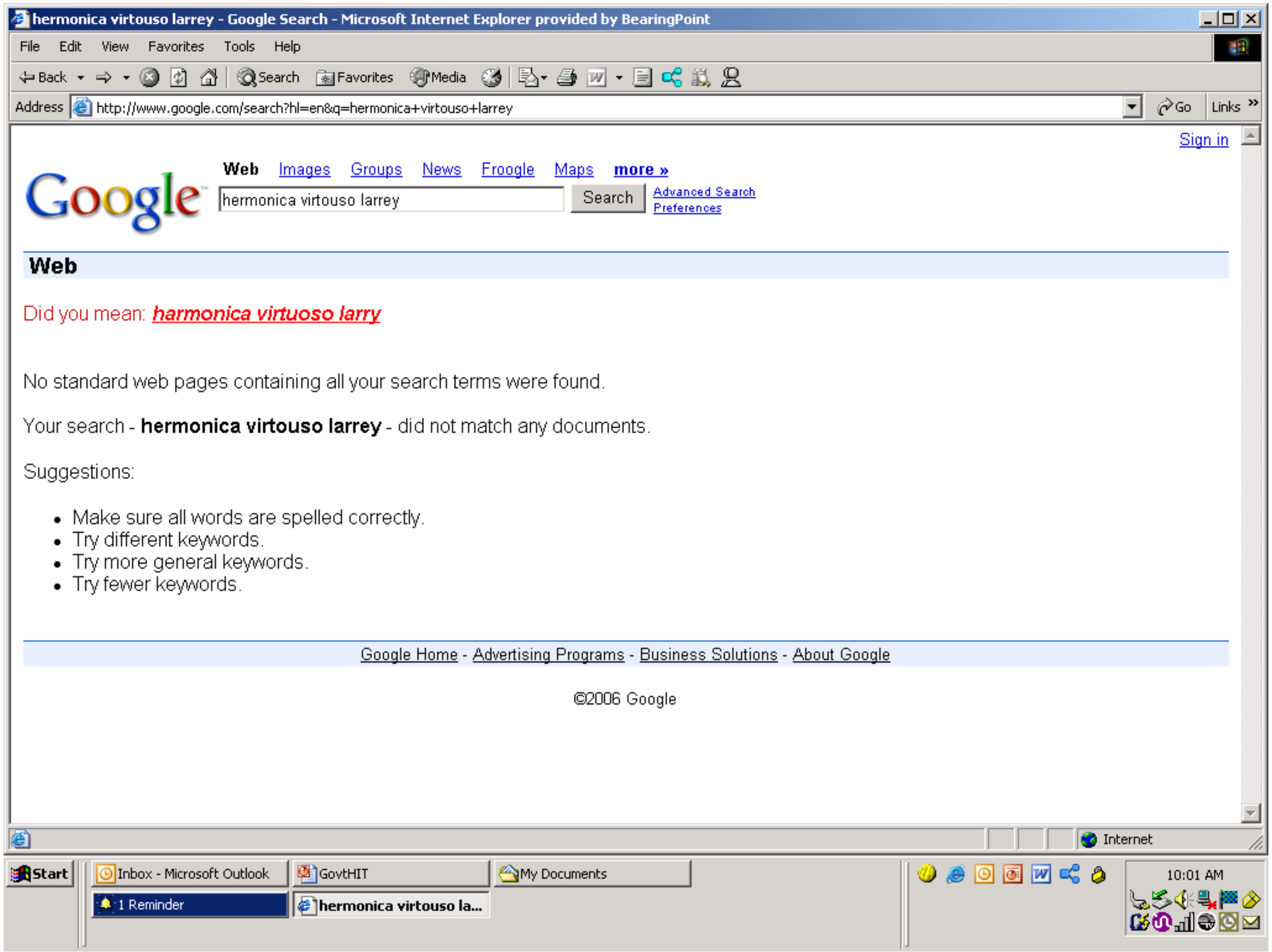
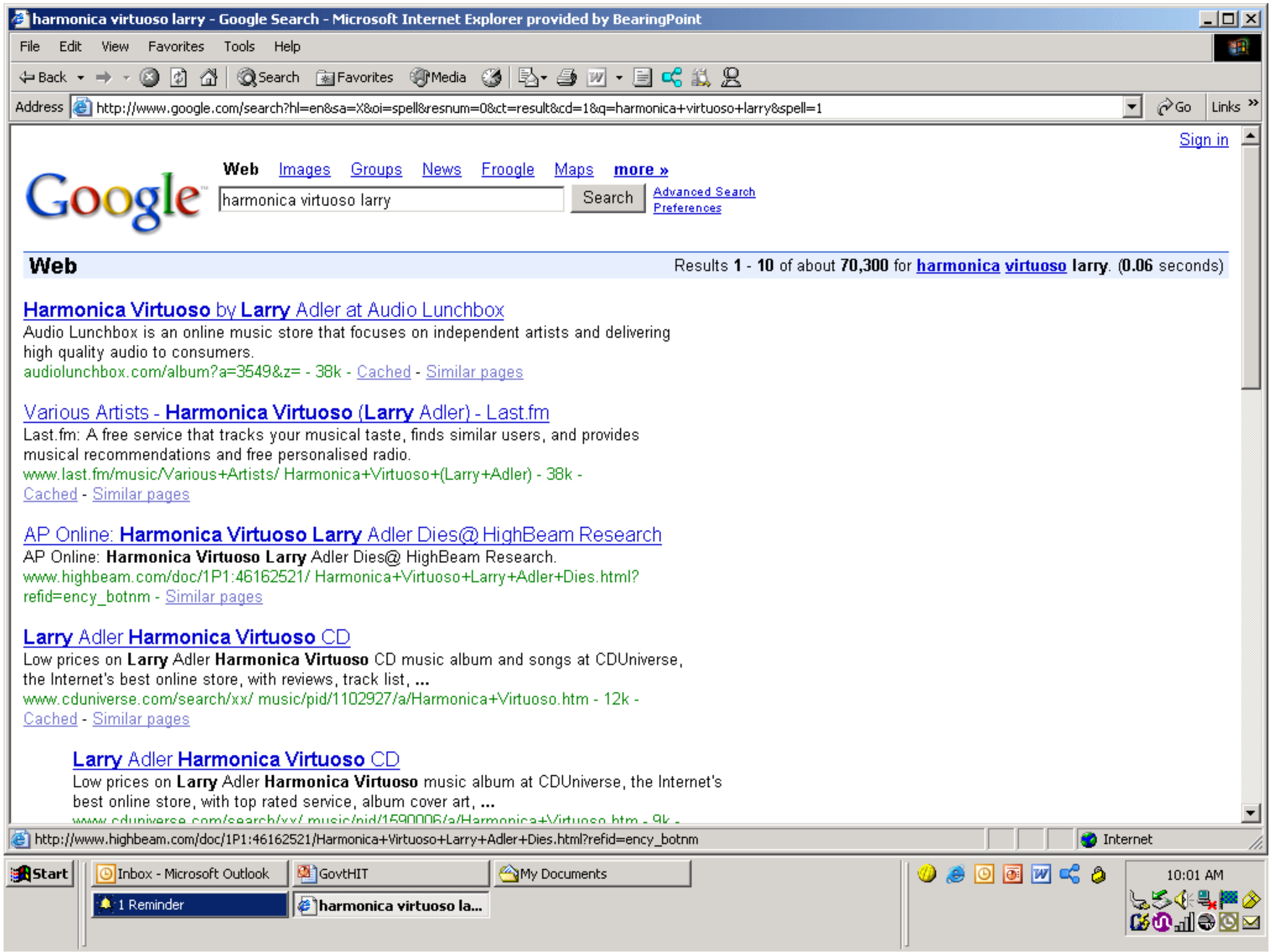
BARKER & RANSOM.

Office open from 6 A. M. to 2 A. M.
After March 1st, this Office will be open all night.

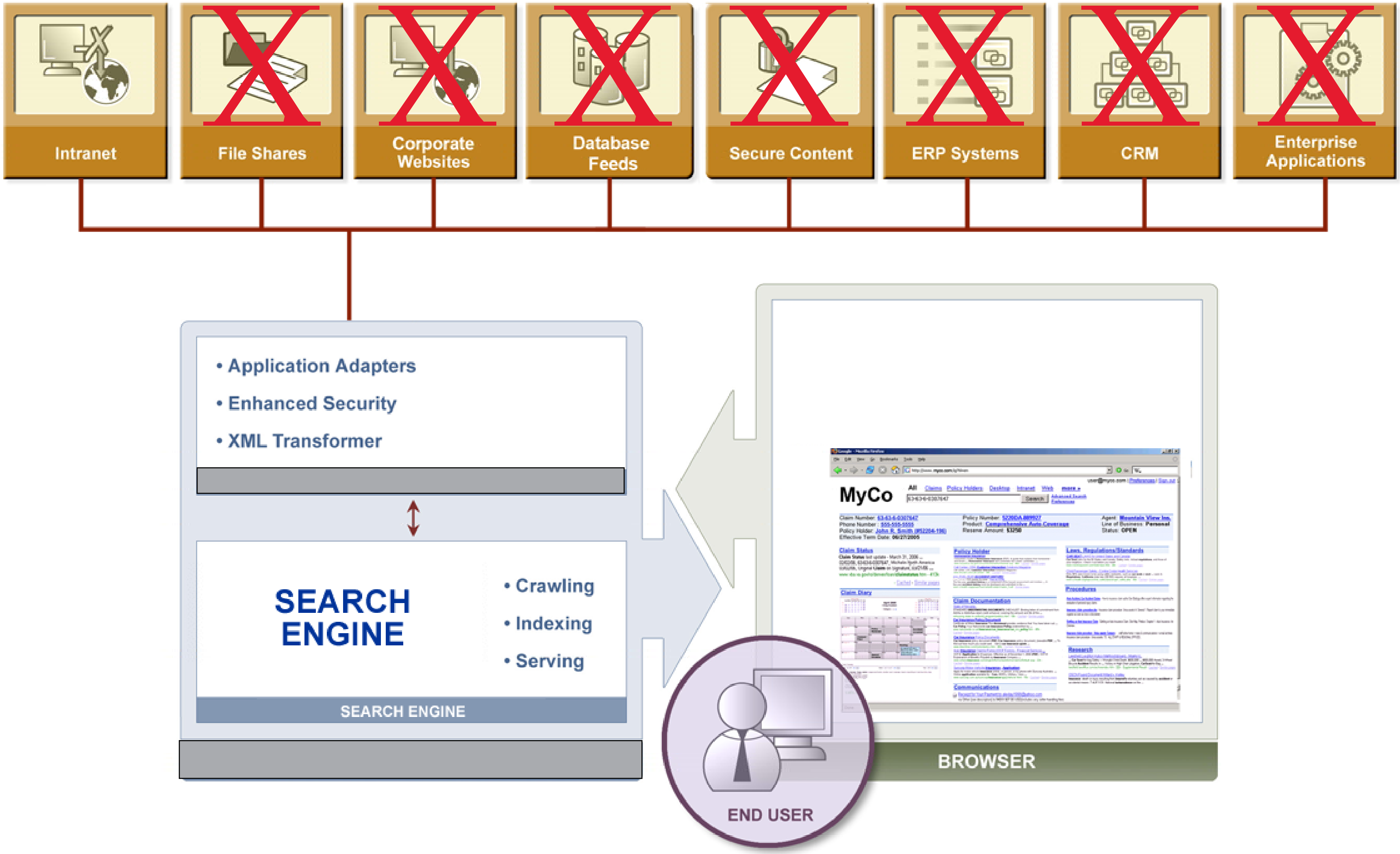
Search Applied to Crossword Puzzles



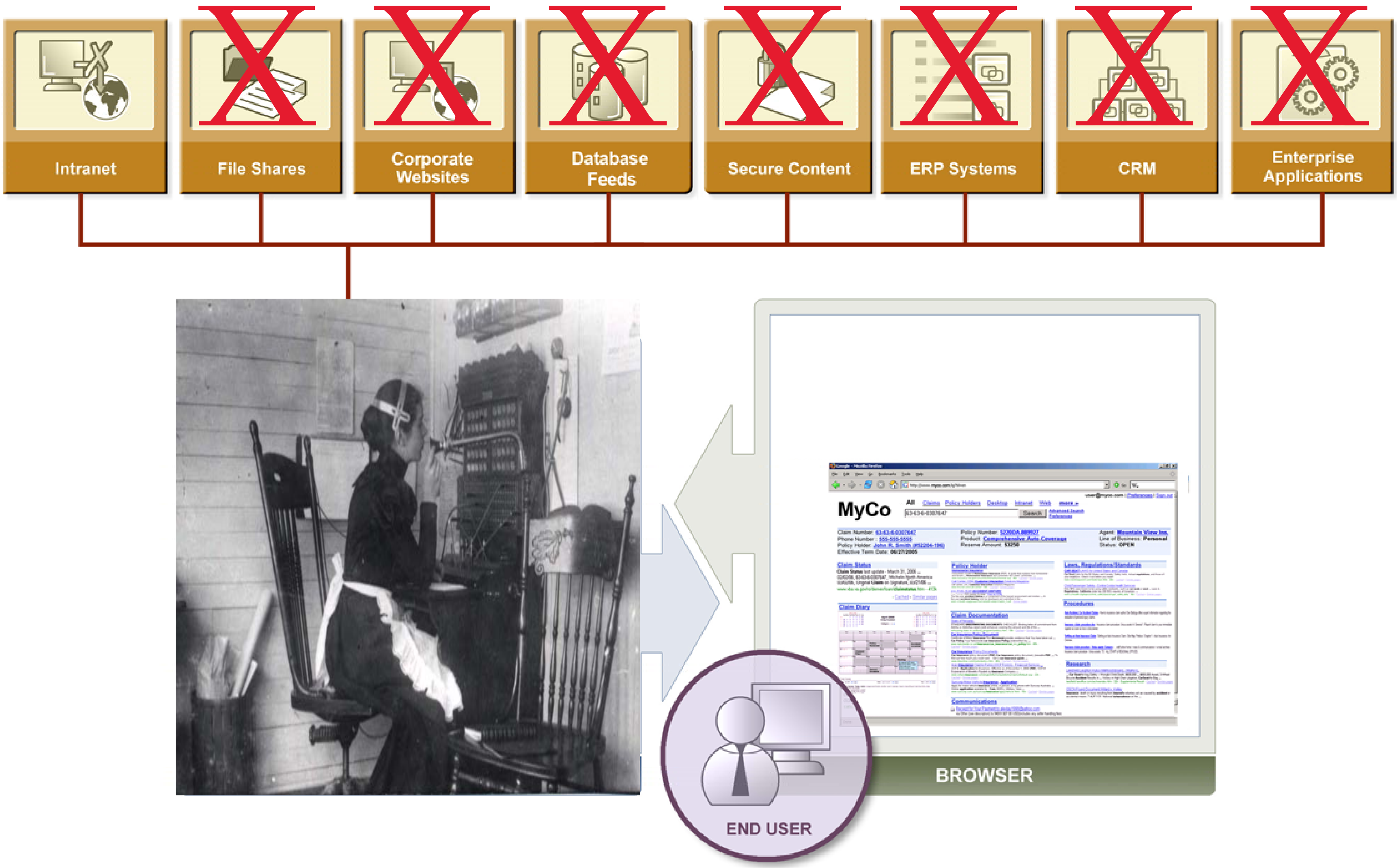
Search Applied to Crossword Puzzles



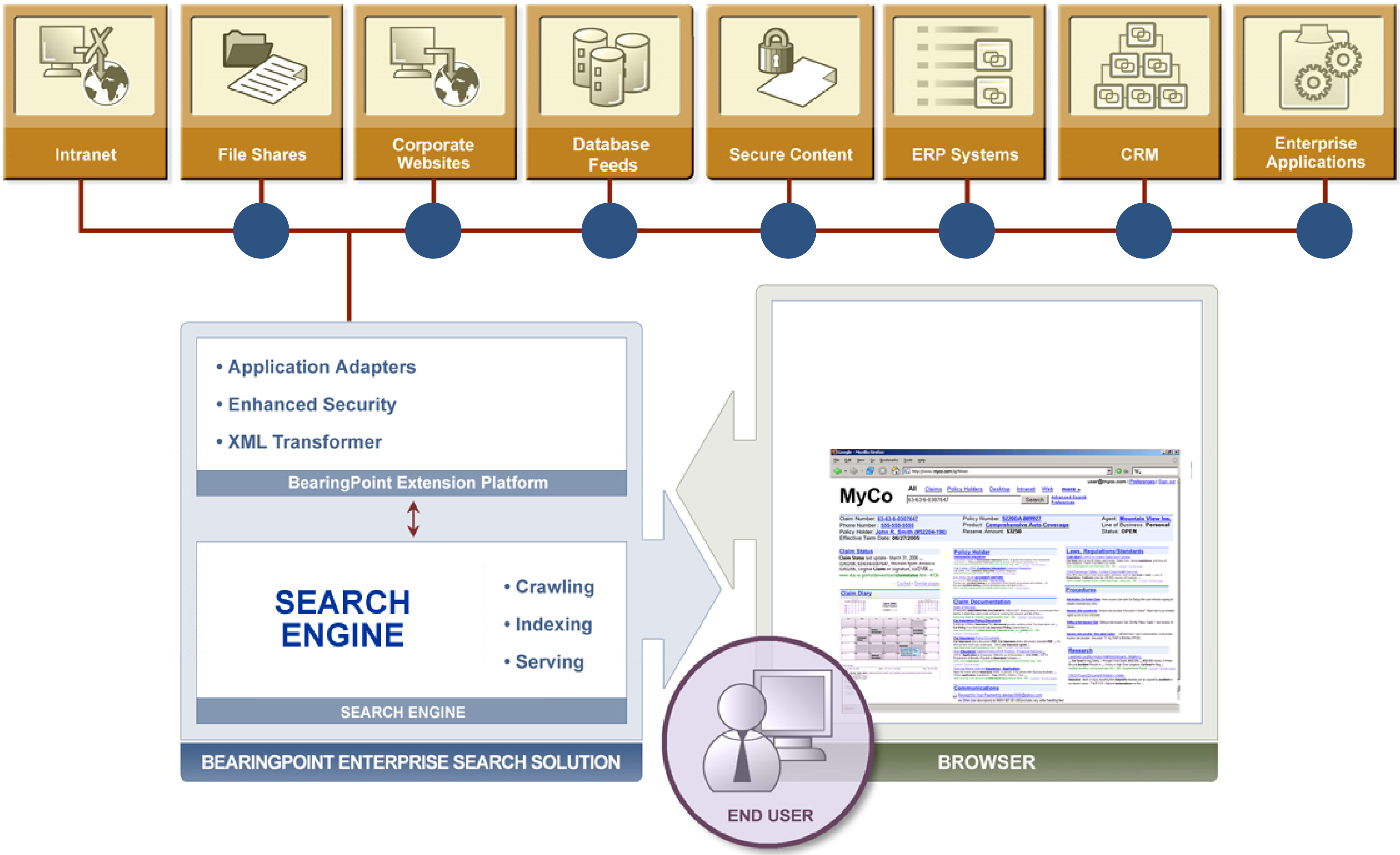
Enterprise Search Solutions: Native Capability



Enterprise Search Solutions: Native Capability



Enterprise Search Solutions Enabled by Software Adapters: "●"



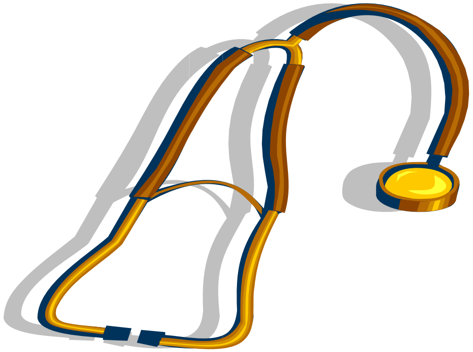
Anonymous Observation on a New Technology

"That it will ever come into general use, not withstanding its value,
is extremely doubtful because its beneficial application requires much time and gives a good bit of trouble, both to the patient and to the practitioner..."

Anonymous Observation on a New Technology

"That it will ever come into general use, not withstanding its value,
is extremely doubtful because its beneficial application requires much time and gives a good bit of trouble, both to the patient and to the practitioner..."

(The Stethoscope)



Health IT Innovation References

- Healing the 800 Pound Gorilla: Excerpted from "Seeing What's Next: Using the Theories of innovation to Predict Industry Change," C. M. Christensen et al, Harvard Business School Press
- Your Money or Your Life, David Cutler
- Saving Money Saving Lives, Newt Gingrich

BearingPoint®

Technology and Challenges for Minimally Invasive Spine Interventions

Kevin Cleary, PhD

Imaging Science and Information Systems (ISIS) Center

Georgetown University, Washington, DC, USA

2007

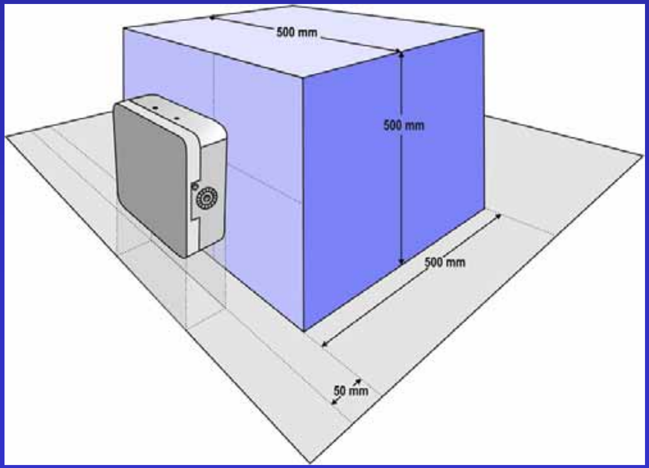
IBMISPS

Washington DC

Overview

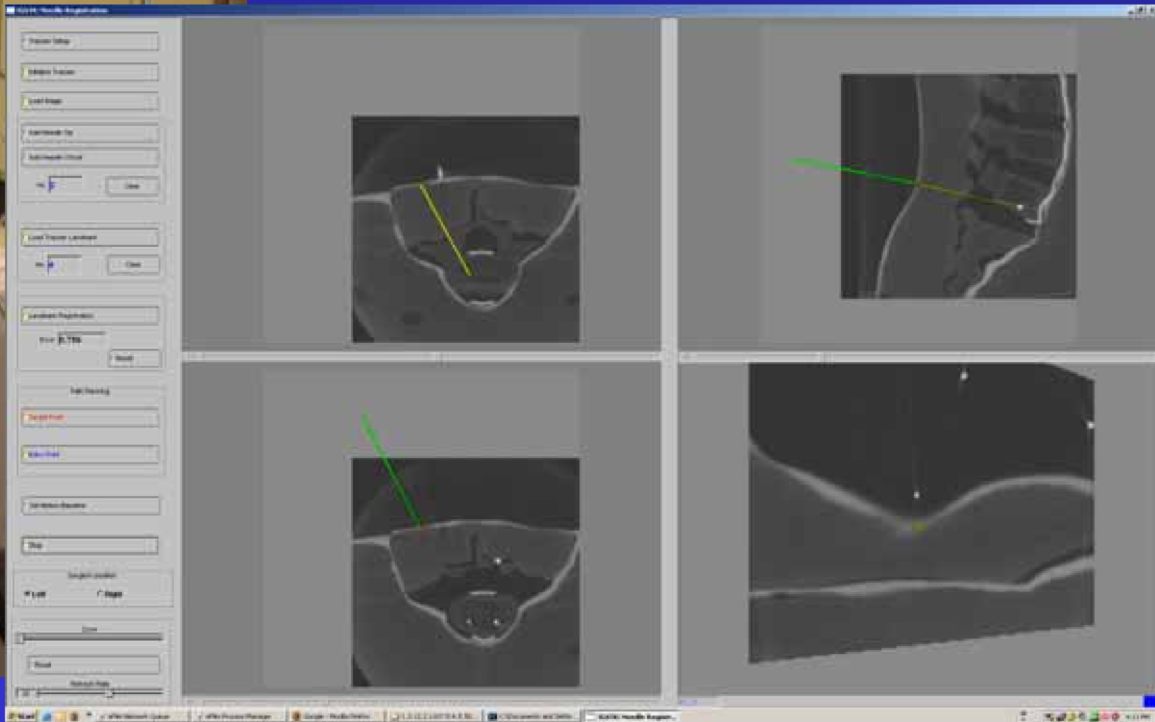
- Instrument tracking and robotically assisted instrument placement can enable minimally invasive spine procedures
- Several example systems will be presented
  - Electromagnetic tracking for vertebroplasty
  - Medical robotics for pedicle screw placement
- The integration of these technologies with intraprocedure imaging may open new possibilities in minimally invasive spine procedures

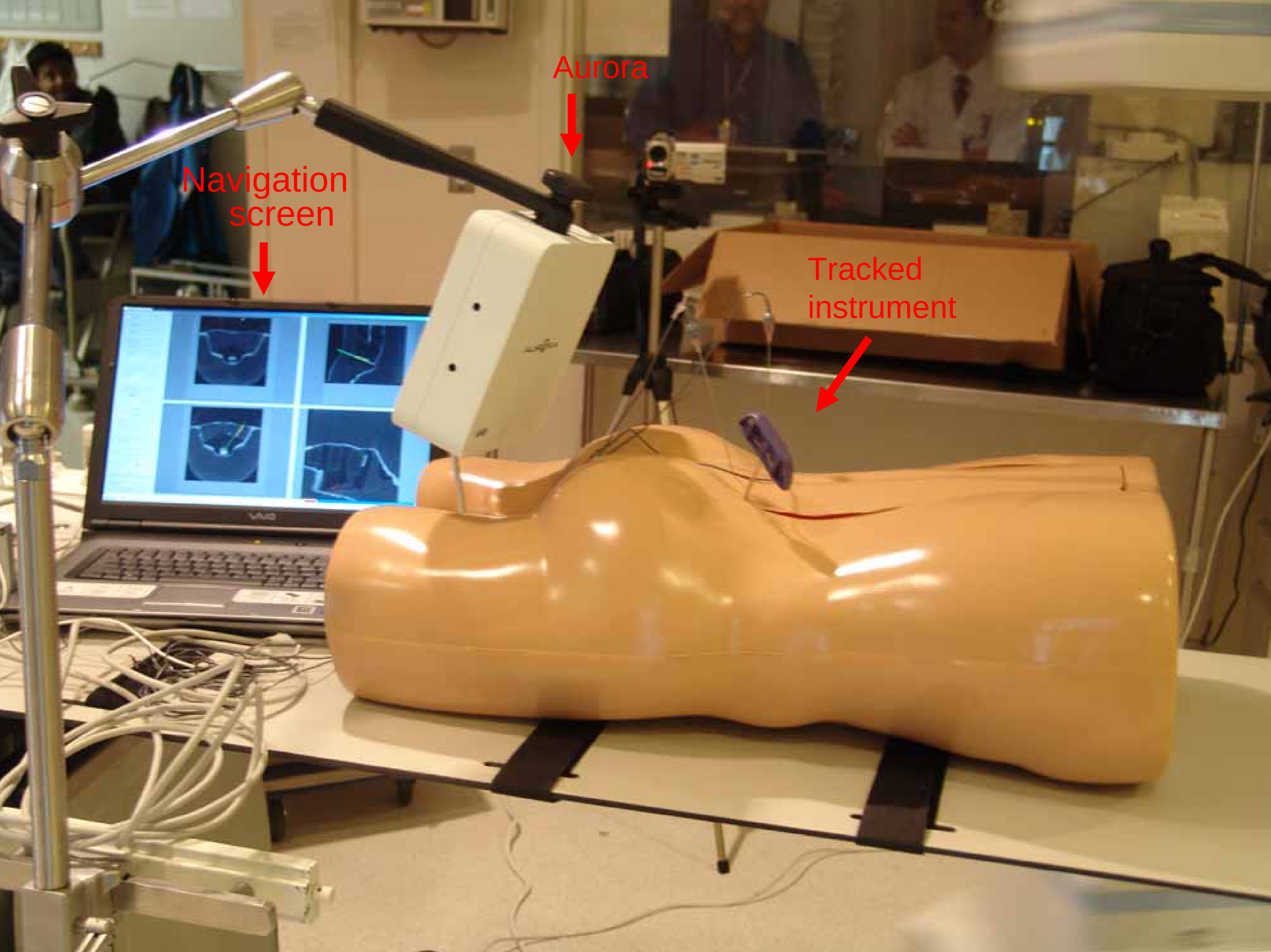
Electromagnetic Tracking

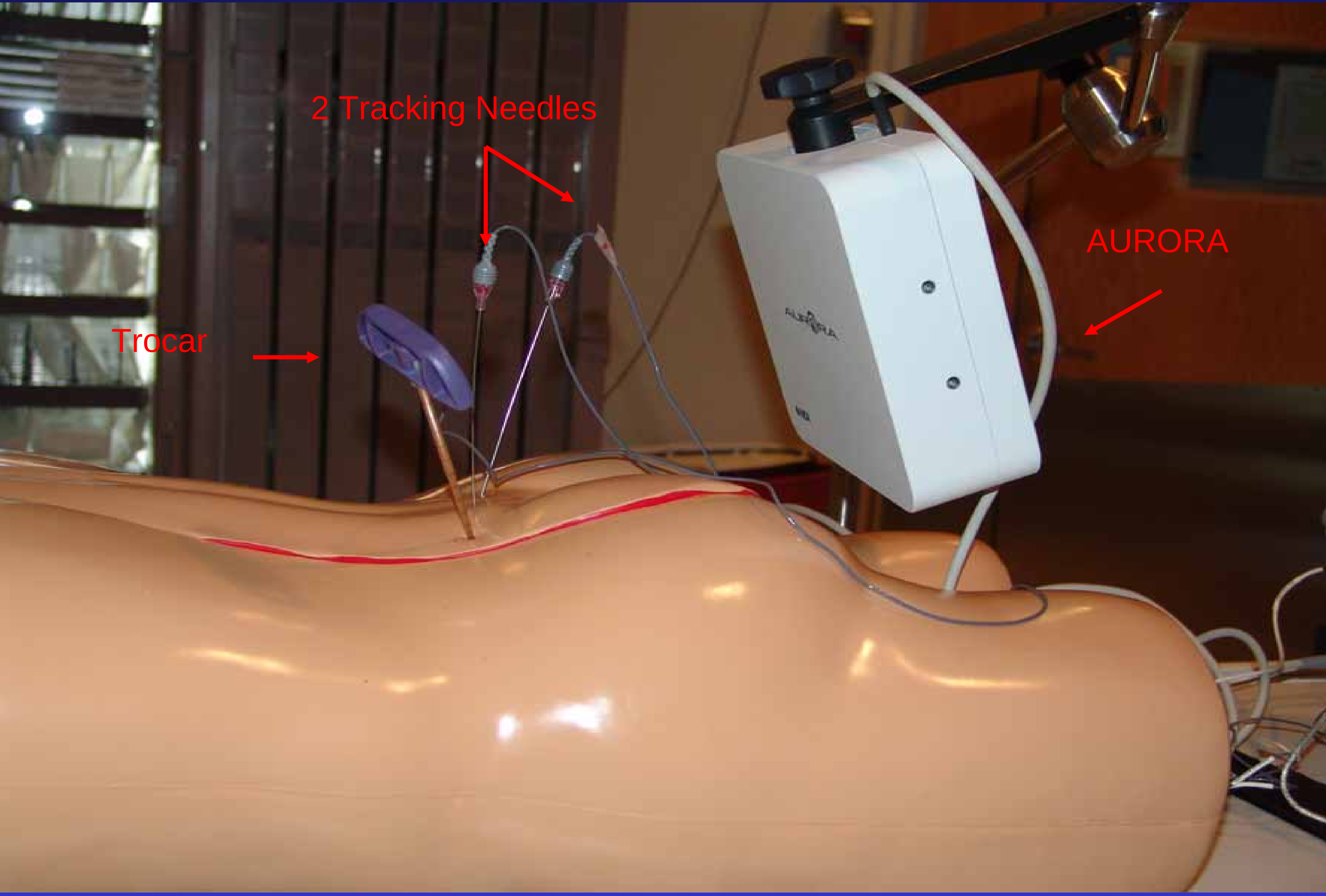


Courtesy of Northern Digital Inc.

Example application Kyphoplasty / Vertebroplasty in spine




Aurora
Navigation screen
Tracked instrument


2 Tracking Needles
Trocar
AURORA

IR2010

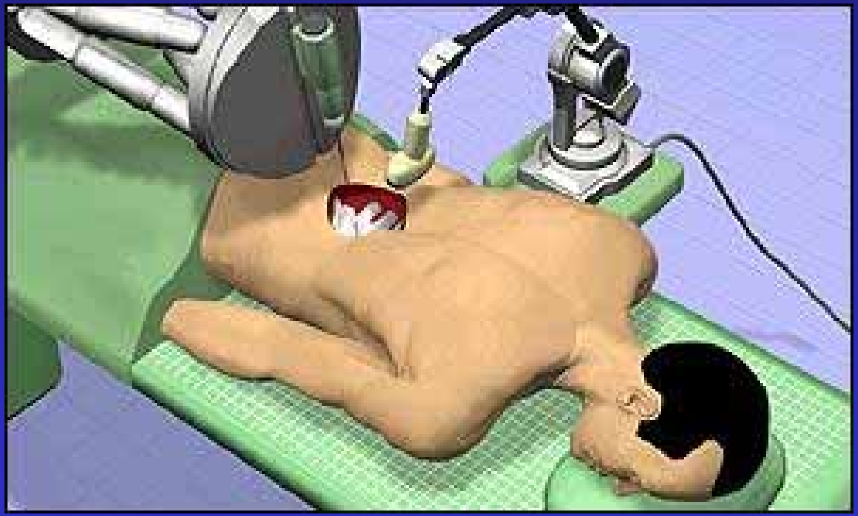
- Interventional Radiology 2010
- “One-stop shopping” – combine diagnosis and therapy
- 3D navigation based on rotational angiography and electromagnetic tracking of instruments and anatomy

Medical Robotics

- Lots of popular press but very little clinical use
- Two market leaders
  - CyberKnife by Accuray
  - Da Vinci by Intuitive Surgical
- Several prototype systems for pedicle screw placement

Pedicle Screw Insertion

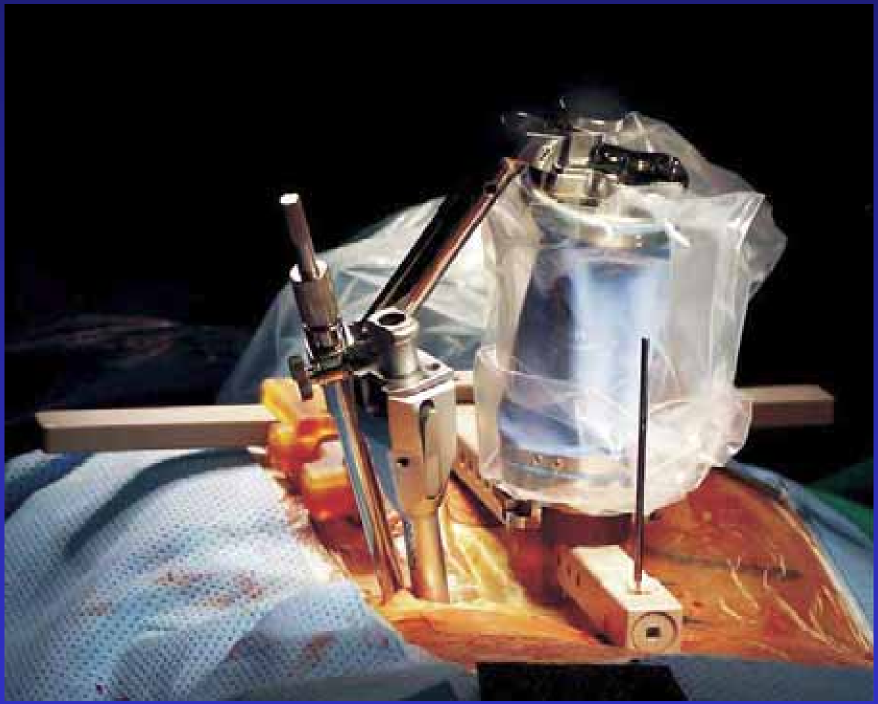
- Parallel robotics mechanism holds screw guide
- Procedure is monitored using ultrasound
- Developed by Fraunhofer Institute for Biomedical Engineering (IBMT) in Germany



From BBC news
http://news.bbc.co.uk/2/hi/health/672815.stm

Spine Assist Robot

- Miniature robot that attaches directly to spine
- Provides guidance for vertebral procedures
- Interfaces with C-arm imaging



From SpineAssist brochure
http://www.mazorst.com/

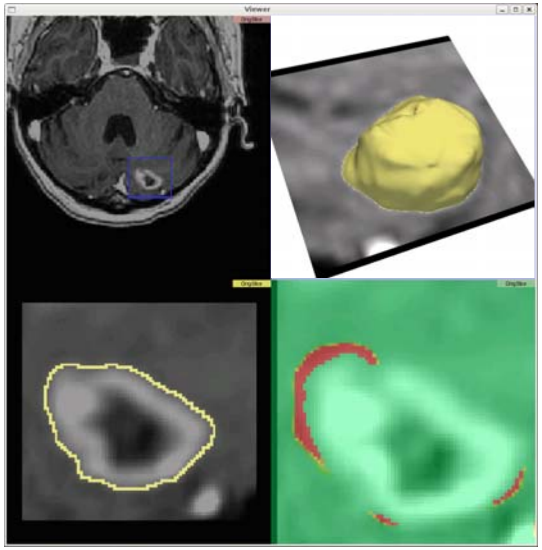
Acknowledgements

- Collaborators
  - Kenneth Wong, PhD
  - Ziv Yaniv, PhD
  - Patrick Cheng, MS
  - Emmanuel Wilson, MS
  - Filip Banovac, MD
  - Vance Watson, MD
- Funding
  - National Institute of Biomedical Imaging and Bioengineering (NIBIB) at the National Institutes of Health (NIH) under grant R42EB000374
  - U.S. Army grant W81XWH-04-1-0078

Surgical Planning Laboratory
Brigham and Women's Hospital
Boston, Massachusetts USA

a teaching affiliate of
Harvard Medical School

MONITORING TUMOR GROWTH

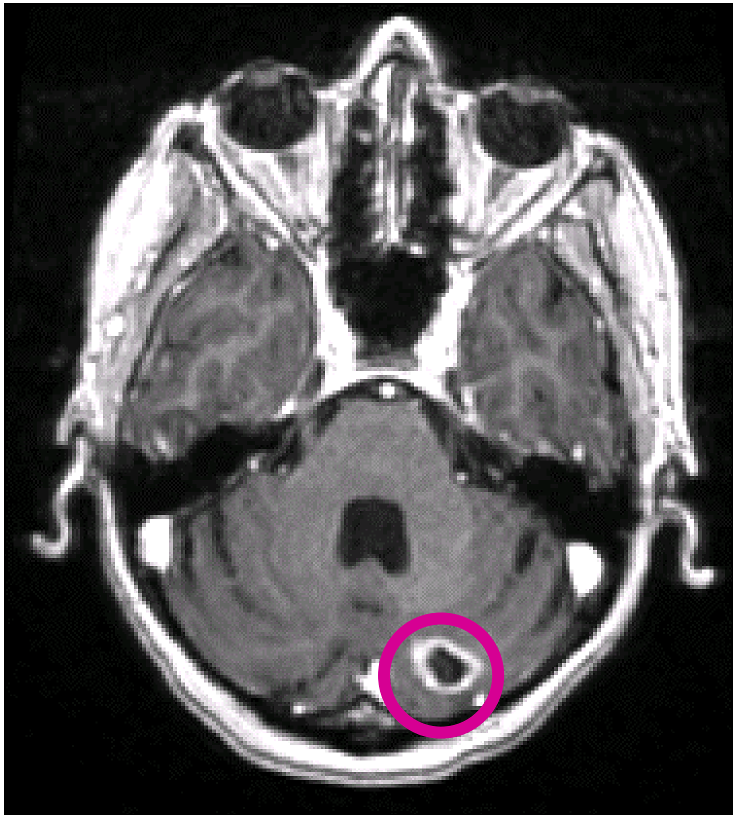


- Ron Kikinis, M.D.,
  Professor of Radiology, HMS
- Kilian Pohl, Ph.D.,
  Instructor in Radiology, HMS

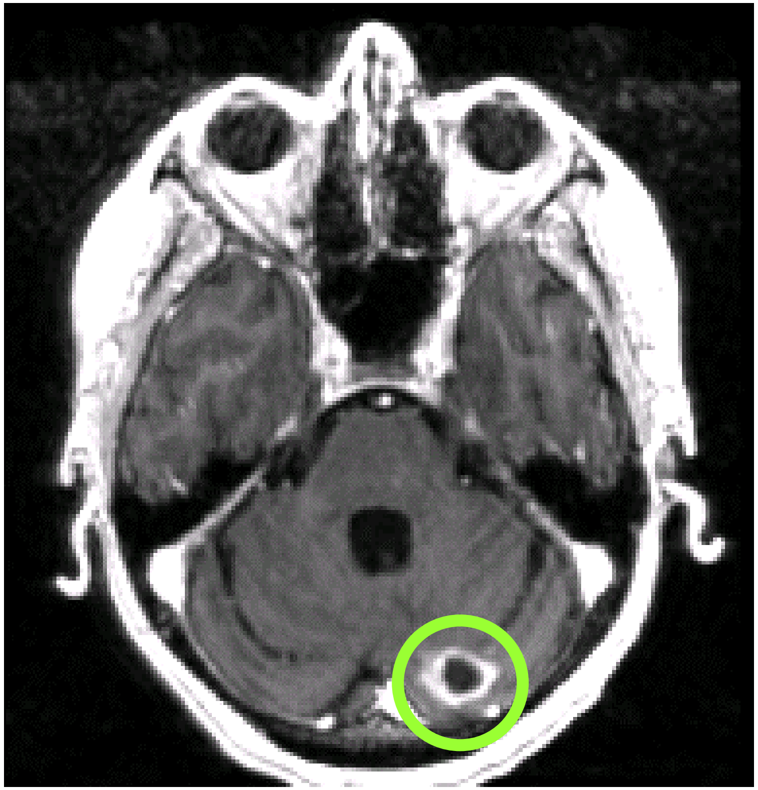
Founding Director, Surgical Planning Laboratory, Brigham and Women's Hospital
Principal Investigator, National Alliance for Medical Image Computing (a National Center for Biomedical Computing, part of the Roadmap Initiative), and Neuroimage Analysis Center (a NCRR National Resource Center)
Research Director, Image Guided Therapy Program, Brigham and Women's Hospital

The Problem

1st Scan



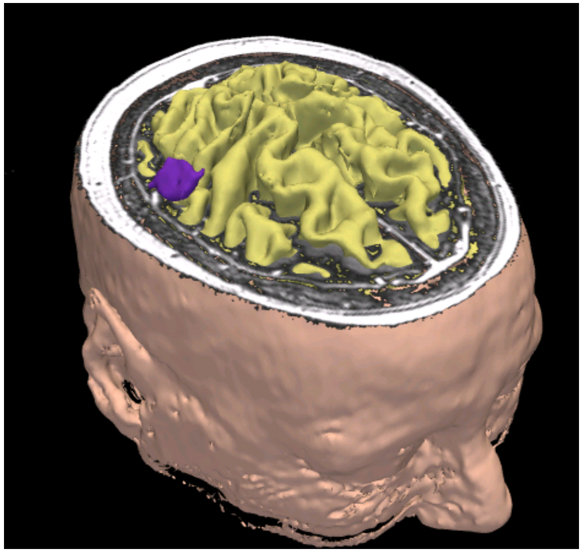
2nd Scan



Has this tumor grown?

Objectives

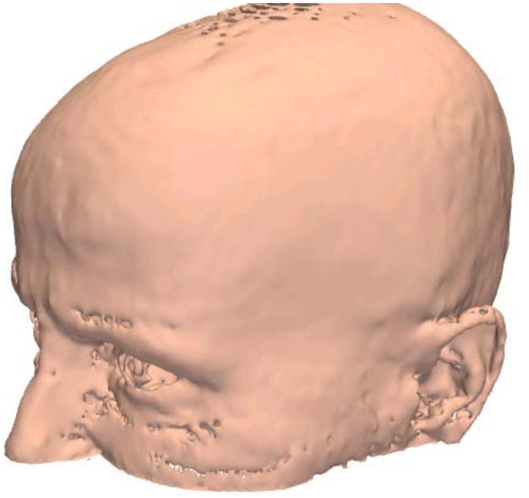
- Meningiomas are often monitored without surgery
- Growth is slow and difficult to assess by visual inspection of consecutive scans
- We developed a software to aid in the assessment of consecutive scans in subjects with brain tumors.



Imaging

Developed a protocol that is compatible with clinical work and can be used for image analysis

- AX 3D SPGR T1 POST
- Voxel dimension: 0.94mm x 0.94mm x 1.20mm
- FOV: 240mm Matrix: 256 x 256
- Slice Thickness: 1.2mm
- Scan time: 8 mins



Prototype User-Interface

Interface in 3D Slicer is based on workflow technology

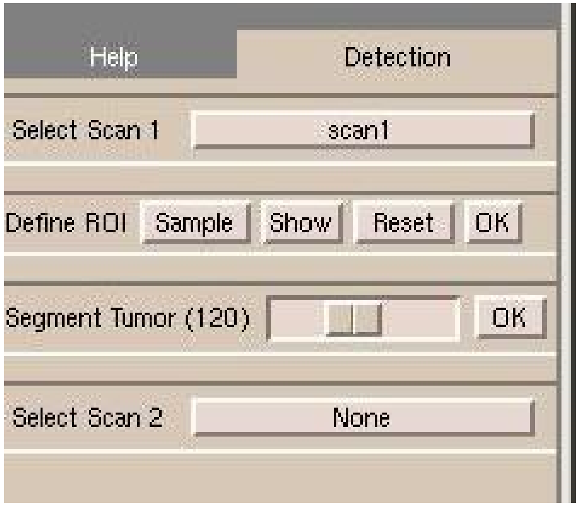
Step 1: Select first scan

Step 2: Define tumor region

Step 3: Segment tumor

Step 4: Select second scan

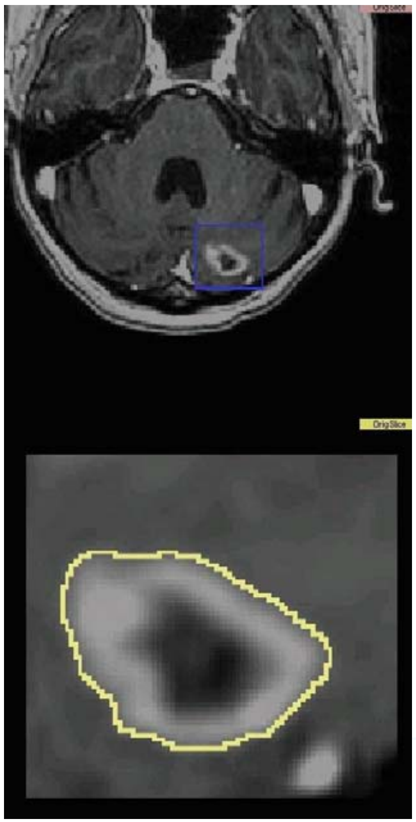
Afterwards, the tool automatically detects any growth in the tumor



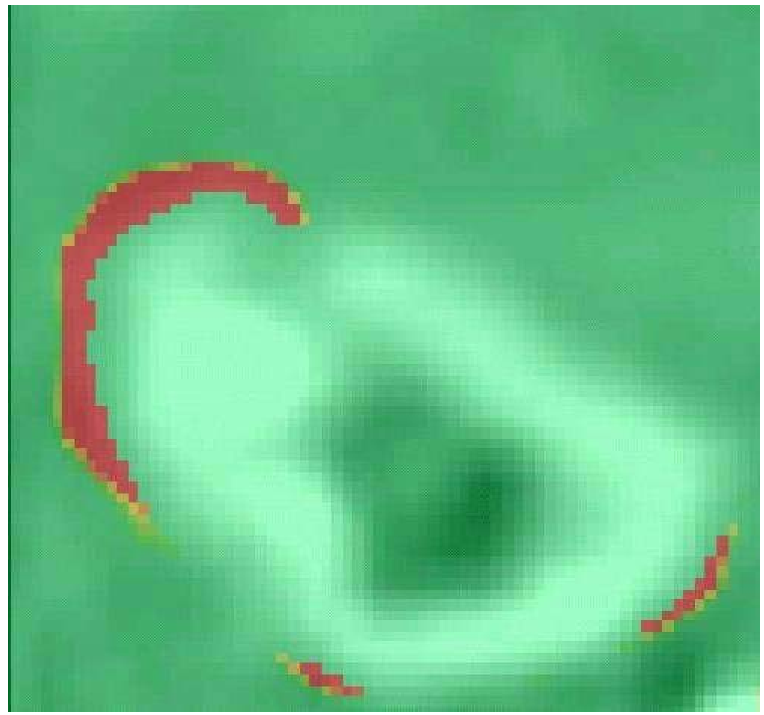
The procedure is completed in less then 5 minutes

Preliminary Results: Cerebellar Metastasis

Scan 1

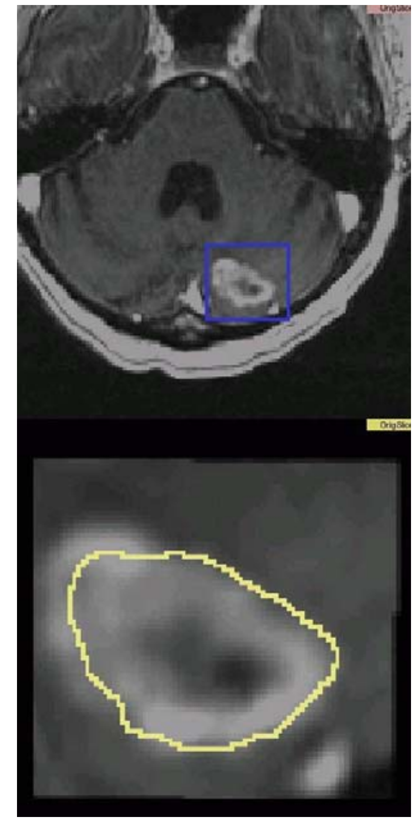


Analysis

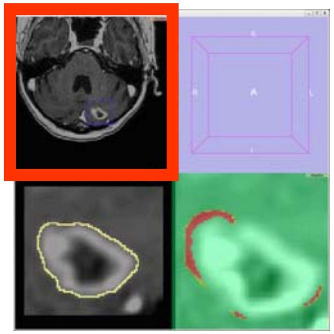


No Change  Growth

Scan 2

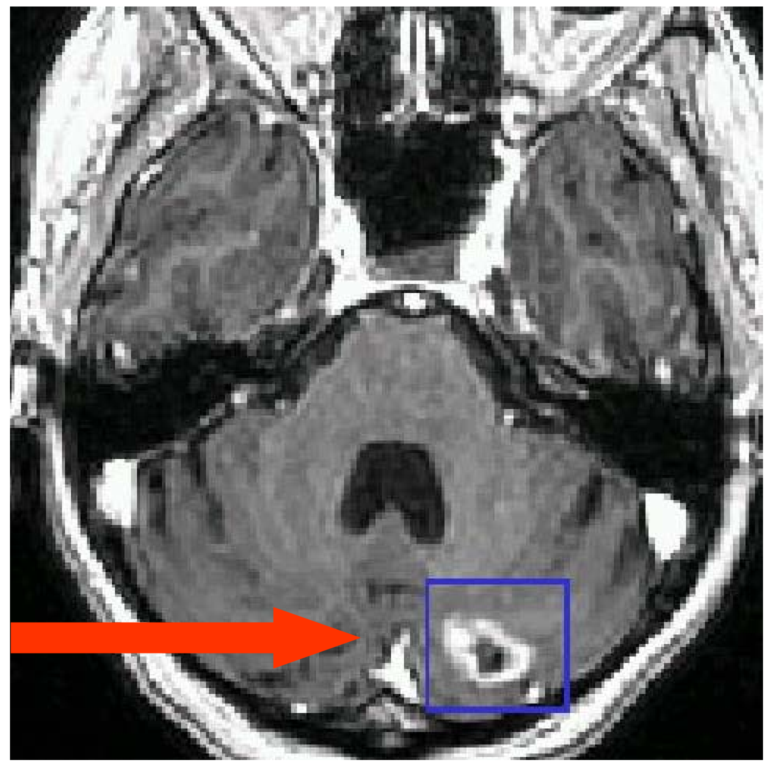


1. Step of Workflow

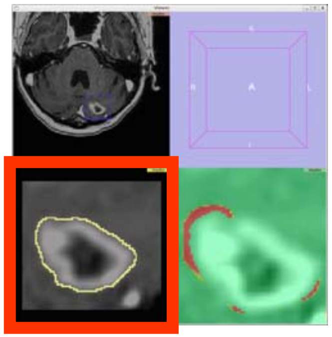


Select Tumor Region in 1st Scan

Simple mouse click around the tumor defines region

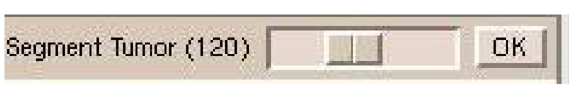


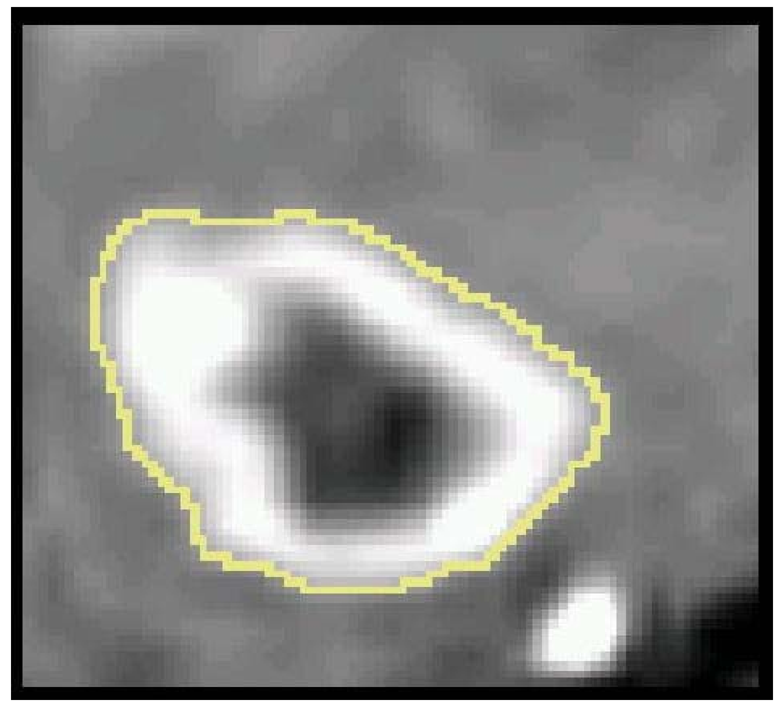
2. Step of Workflow



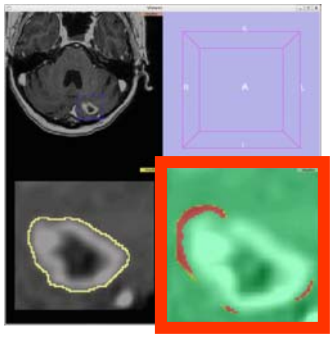
Semi-automatic Segmentation

The state of the art semi-automatic segmenter is calibrated by simply moving a slider



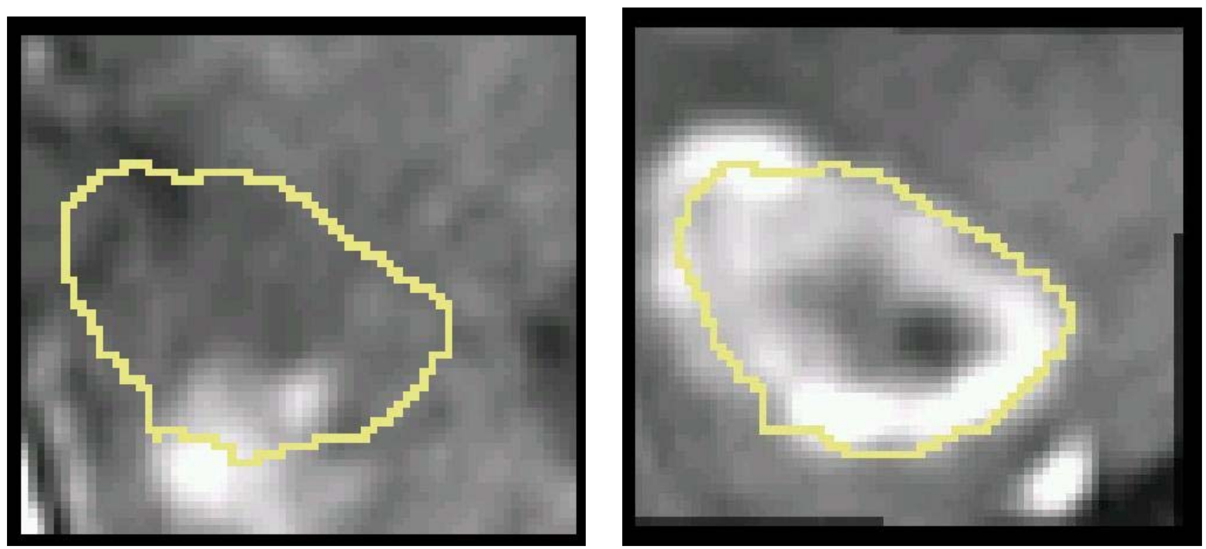


3. Step of Workflow



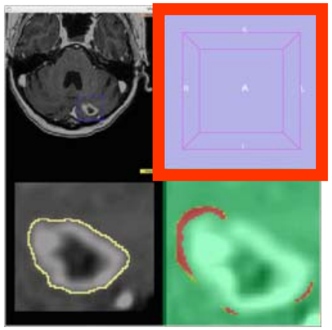
Register 2nd to 1st Scan

We combine global with local rigid registration

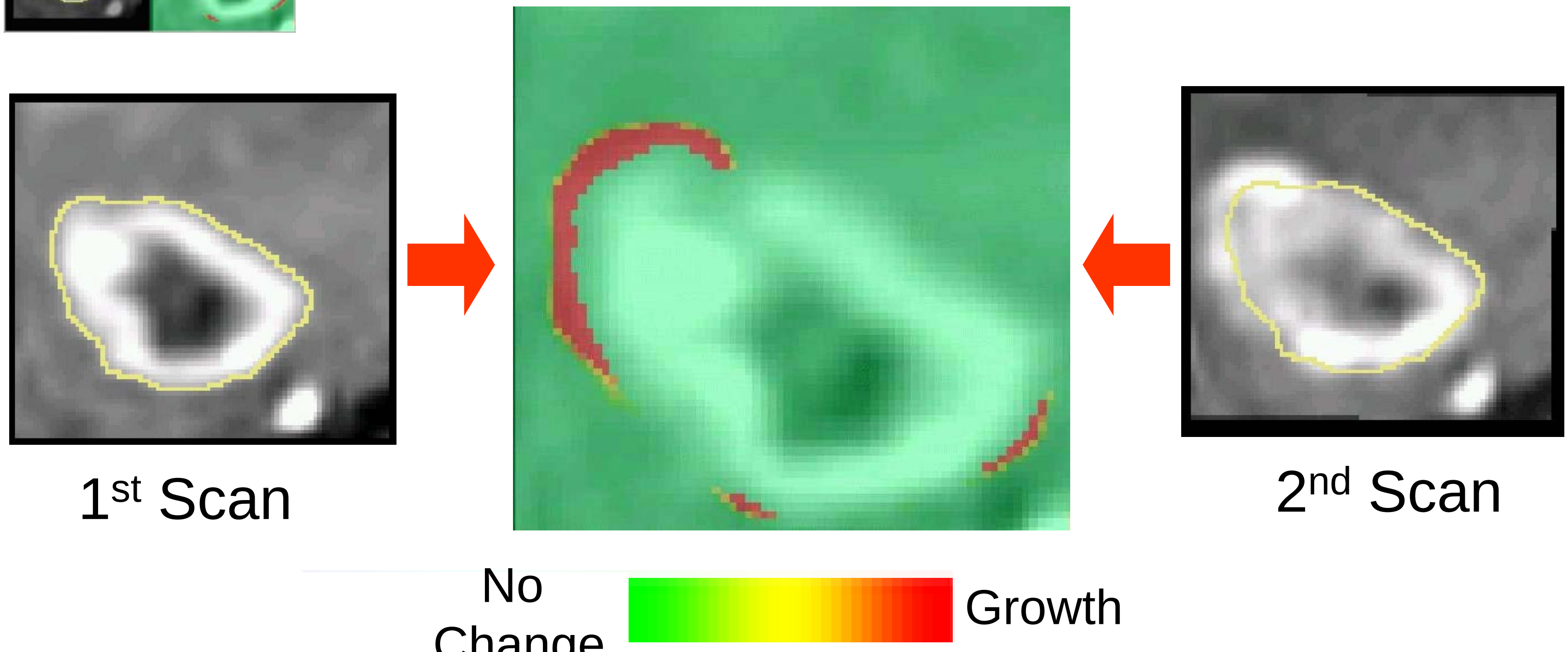


Before | After

4. Step of Workflow

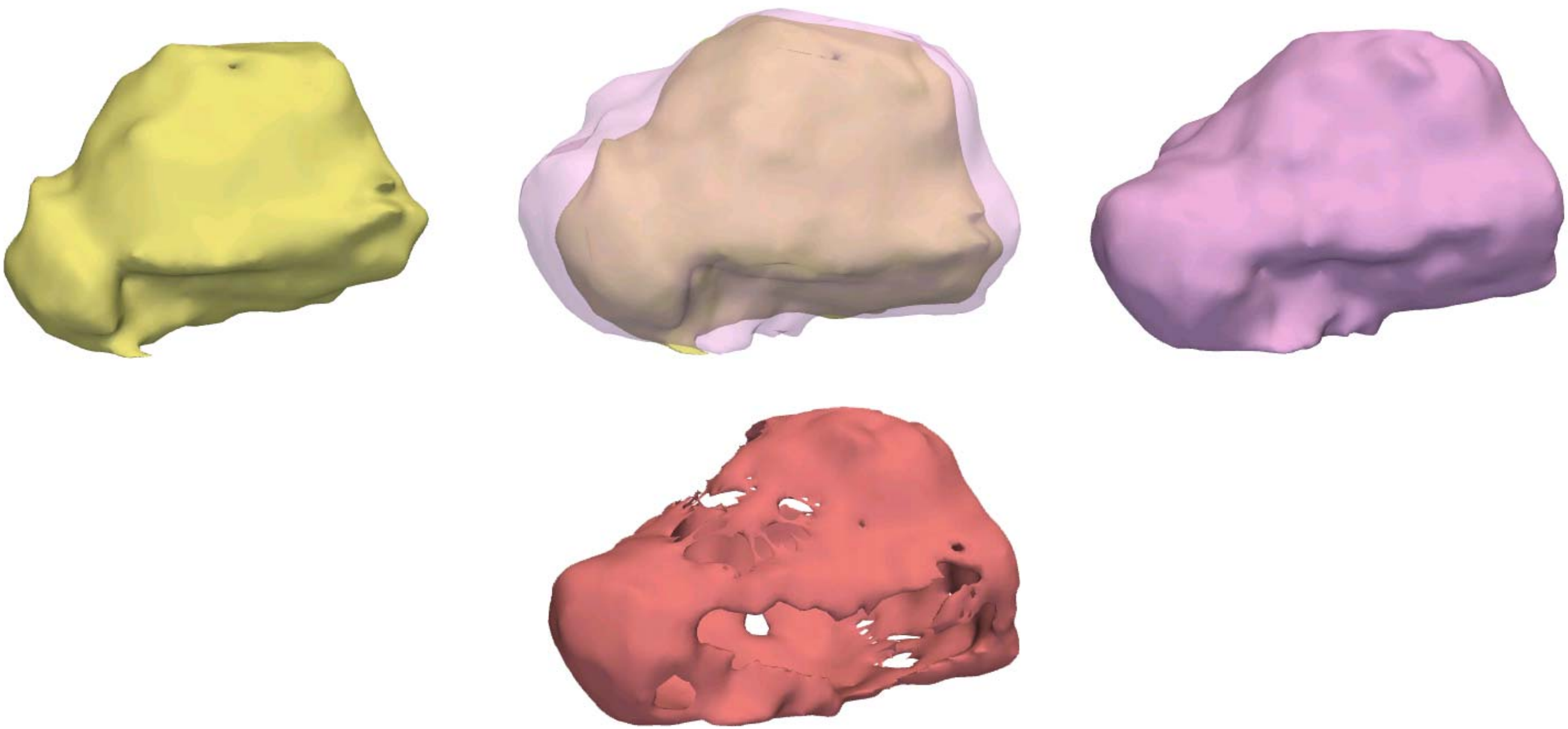


Show and Measure Growth



Detecting Growth in Metastatic Tumor

Scan 1 | Overlap | Scan 2



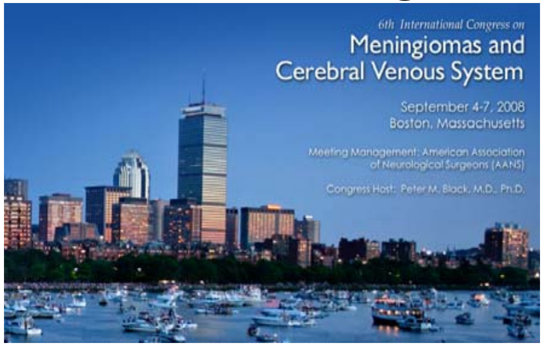
Number of Cases Acquired

The data base consists of

- 5 meningioma and 1 metastatic tumor case with 1 scan using our protocol (BTS)
- 2 metastatic cases with BTS scans at 2 time points
- 1 meningioma case with 3 BTS scans
- ~50 cases acquired with other protocols were used in evaluation of the segmentation algorithms

Outreach

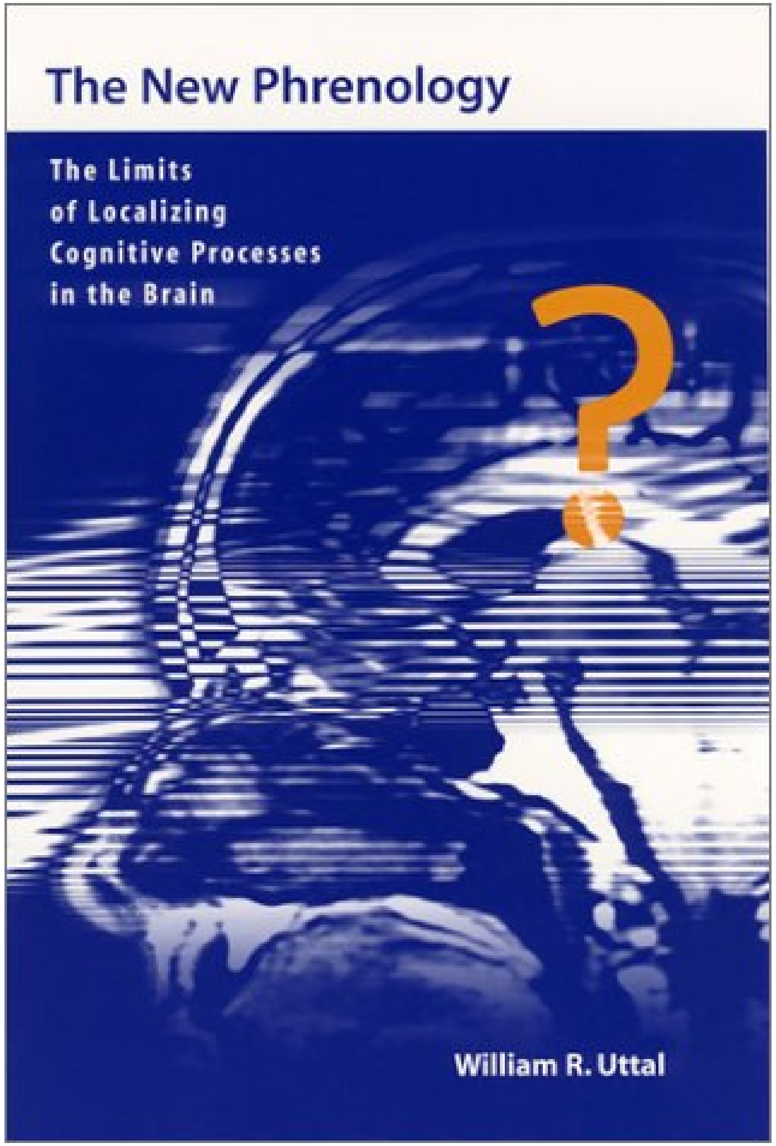
- Further Validate tool
- Make software available for download as part of 3D Slicer (www.slicer.org)
- Outreach event with hands on training during the 6th International Congress on Meningioma: http://www.themeningiomaconference2008.org/



Acknowledgements

- Funding: The Brain Science Foundation
- Neurosurgery: Dr. Black and Kwan Quach
- Radiology: Dr. Zamani and Tuan Luu
- Software: This project leverages a 50+ million dollar investment by NIH.

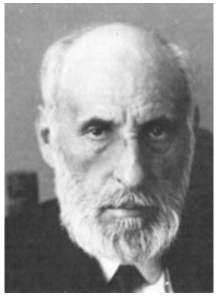
Is fMRI a “New Phrenology“ ?

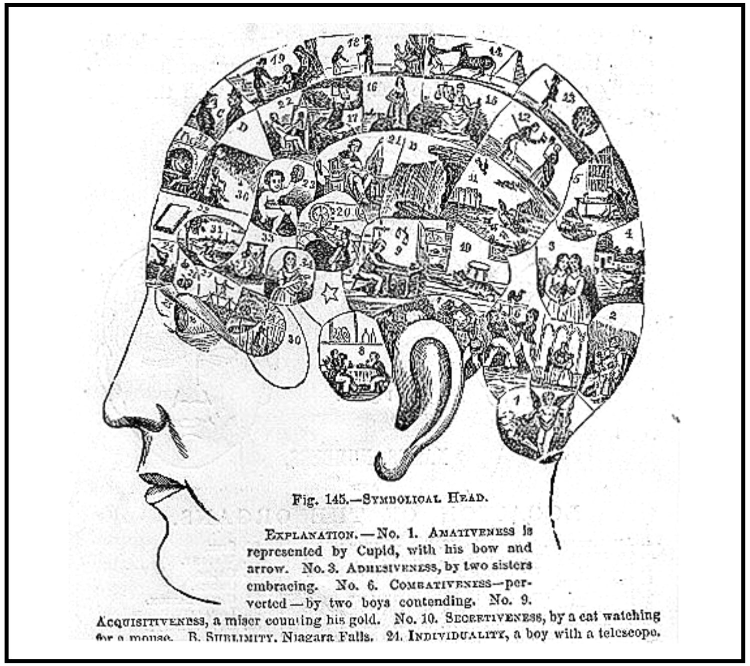


Gall and Cajal

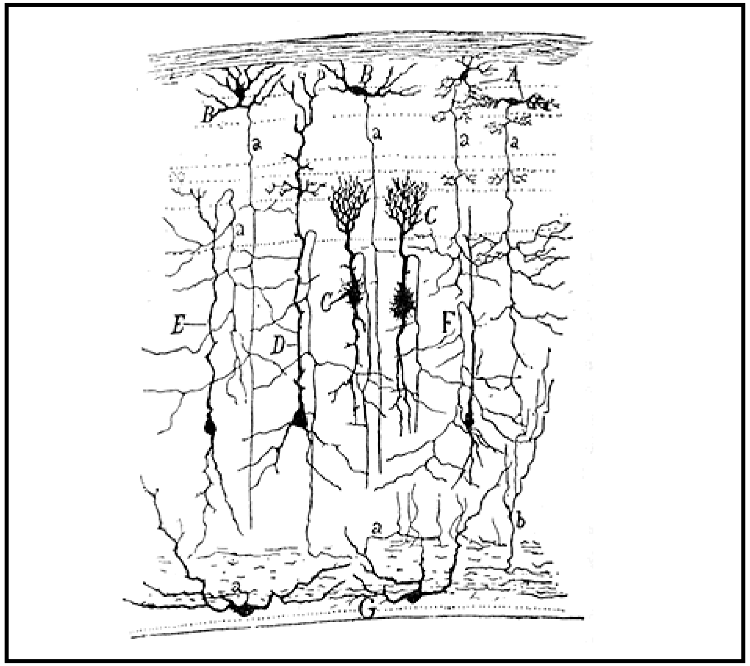
Franz Gall

Ramon Y Cajal





Phrenology



Neurons

Red or Blue Dots in certain brain regions

termed

„Activation" or „Deactivation"

THATS ALL ?????

Red or Blue Dots in certain brain regions

termed

„Activation“ or „Deactivation“

THATS ALL ?????

Is brain function “explained“ by combinations (patterns) of activation/deactivation ?

Red or Blue Dots in certain brain regions

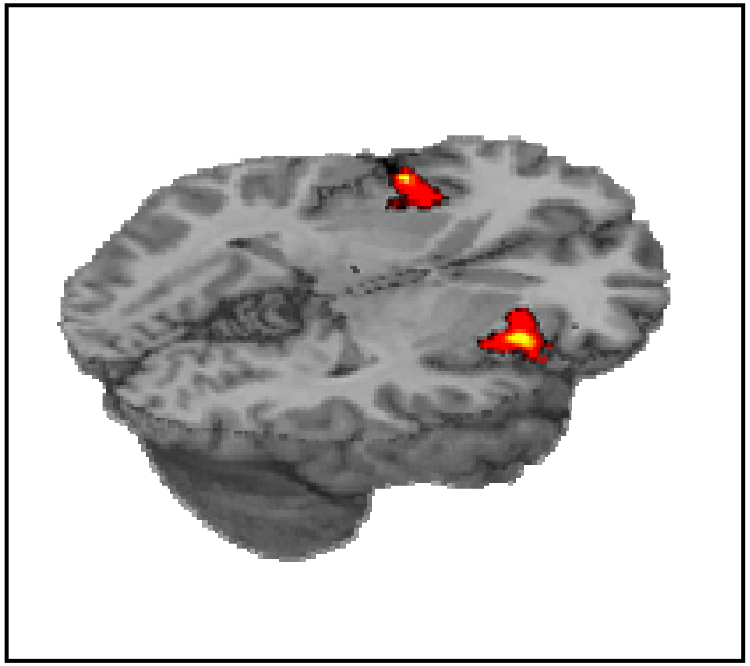
termed

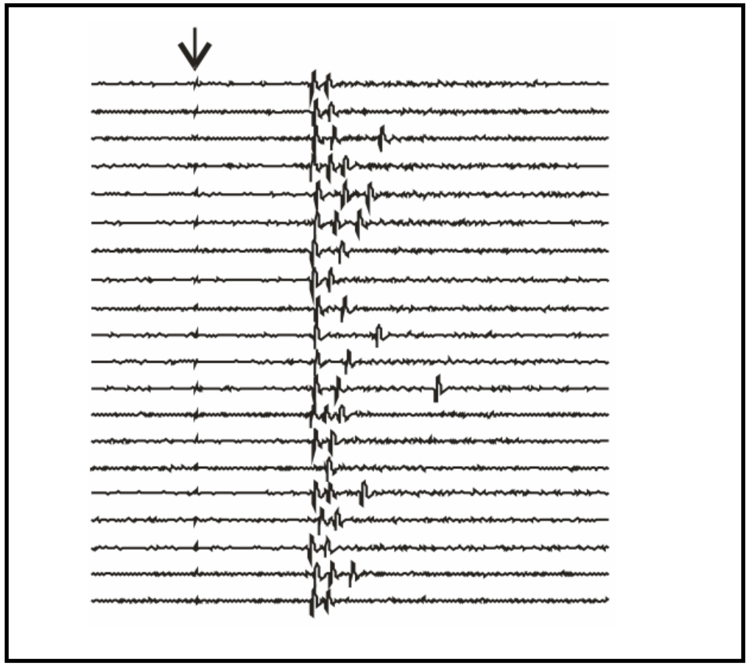
„Activation“ or „Deactivation“

THATS ALL ?????

Do neurons fire more?
Is firing synchronized?
Excitation or Inhibition?

Two Separate Worlds?





Noninvasive
Human fMRI

Invasive
Basic Electrophysiology

or…….?????

……. are there ways to

integrate

fMRI into fundamental neuroscience ?

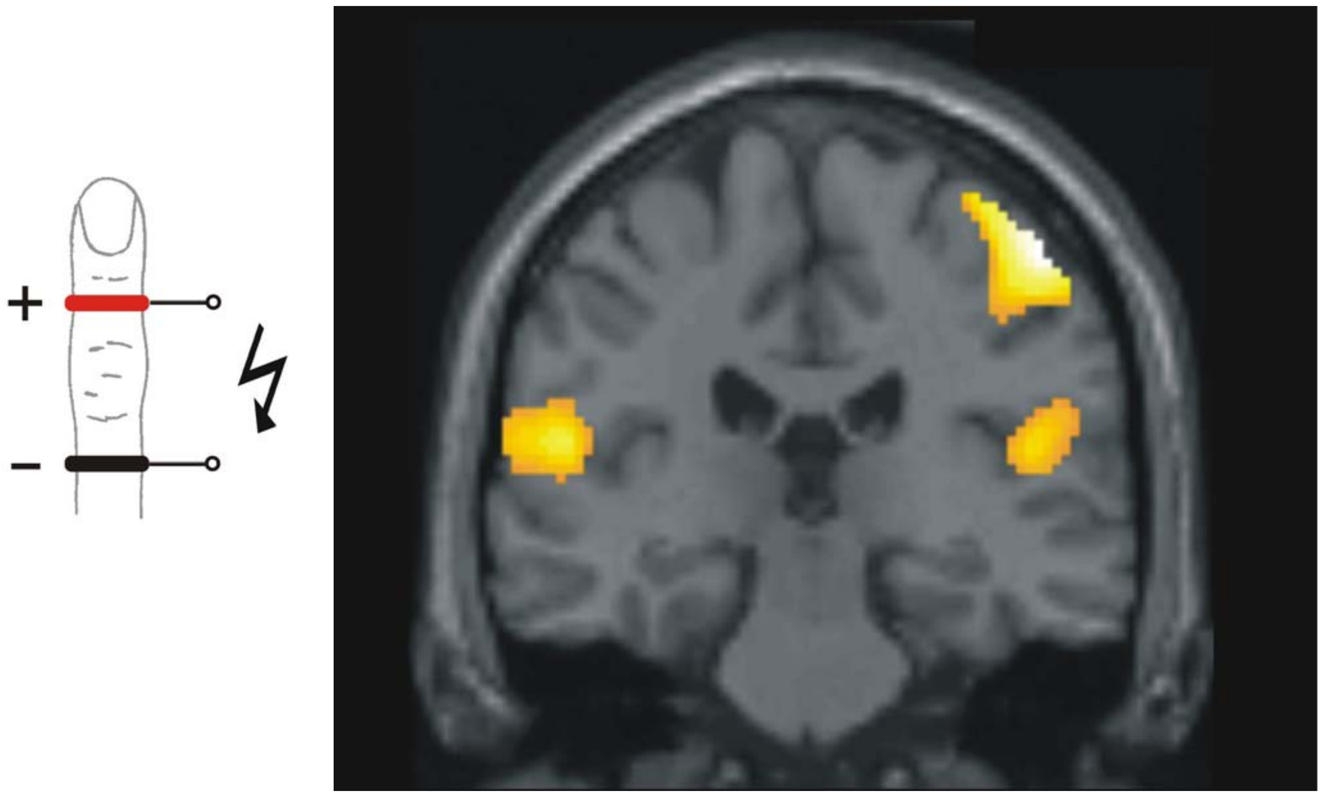
Berlin, May 21, 2007

Aim
Adding physiological meaning to fMRI

"Motto"
"From Gall to Cajal"

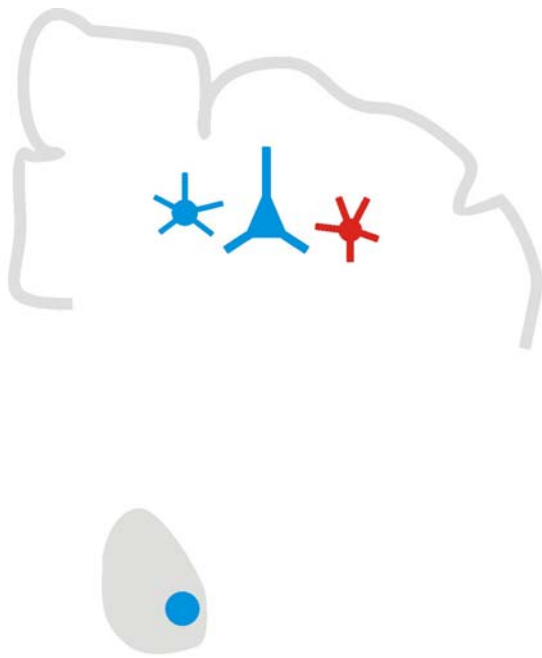
Approach
Multimodal Imaging

Model System
fMRI during Electrical Stimulation of Single Finger

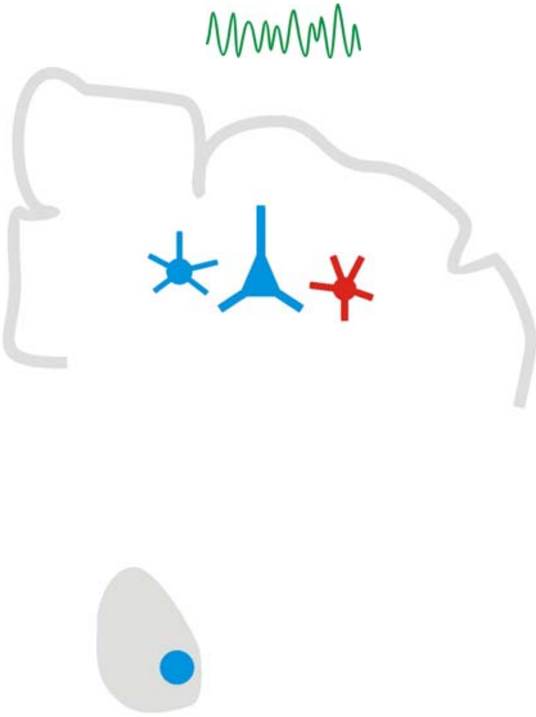


Taskin et al. 2006, Cerebral Cortex

Neurophysiological Events during Somatosensory Processing

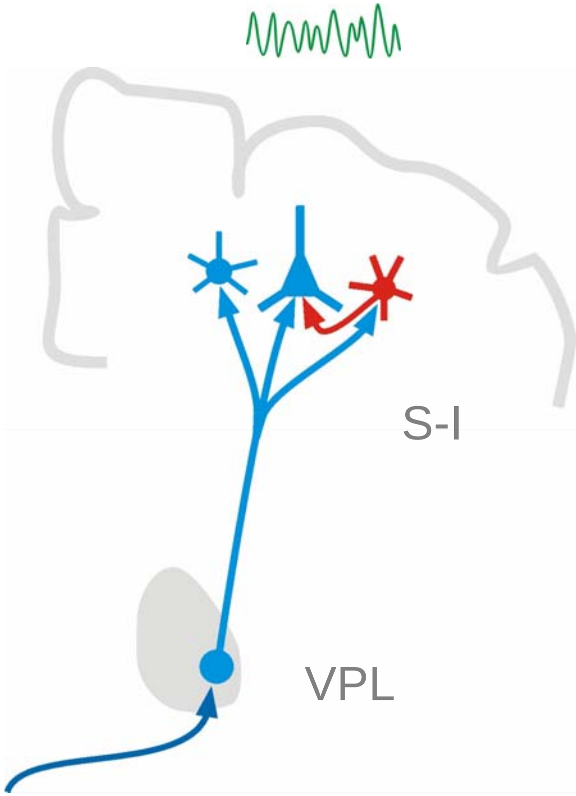


Neurophysiological Events during Somatosensory Processing



Baseline Activity

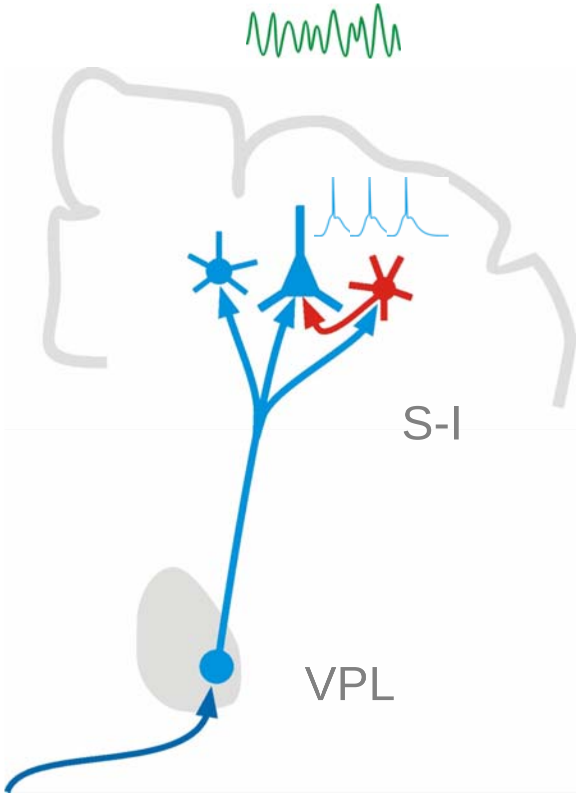
Neurophysiological Events during Somatosensory Processing



Baseline Activity

Excitation / Inhibition

Neurophysiological Events during Somatosensory Processing

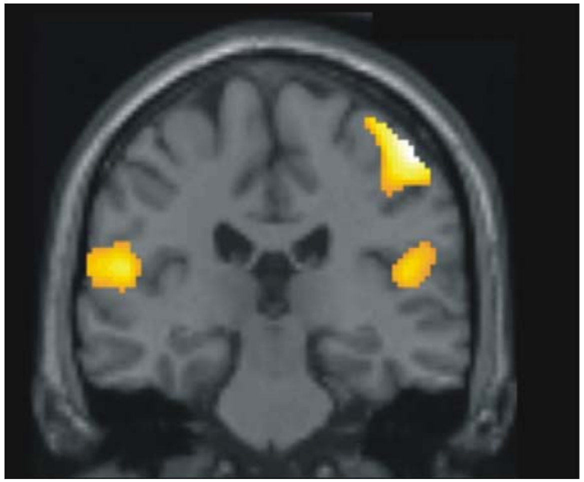


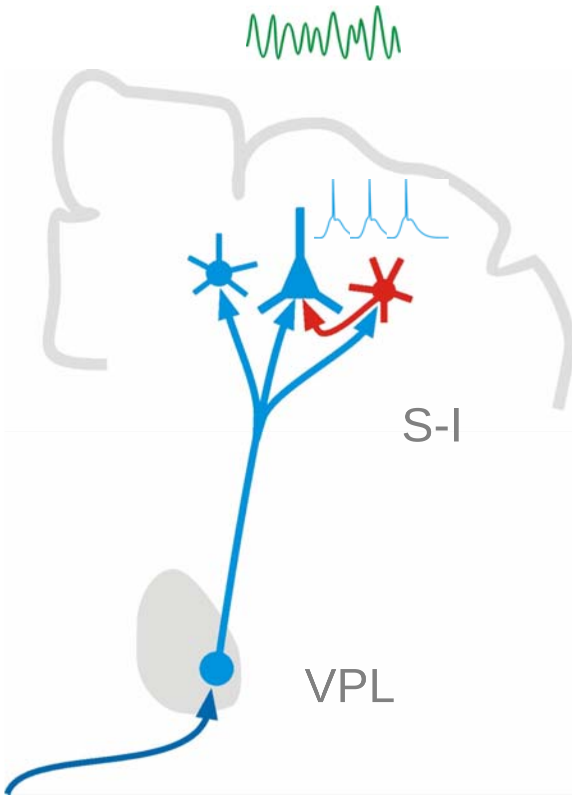
Baseline Activity

Evoked Action Potentials

Excitation / Inhibition

Neurophysiological Events during Somatosensory Processing



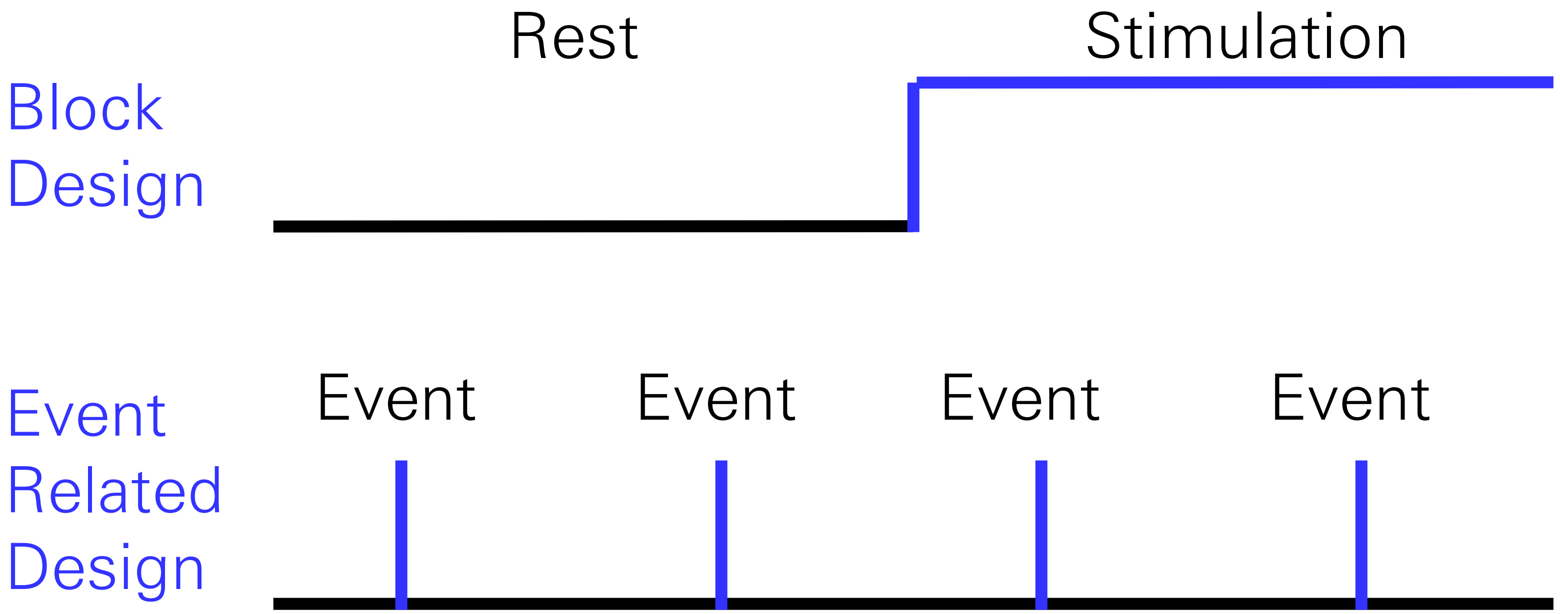


Baseline Activity

Evoked Action Potentials

Excitation / Inhibition

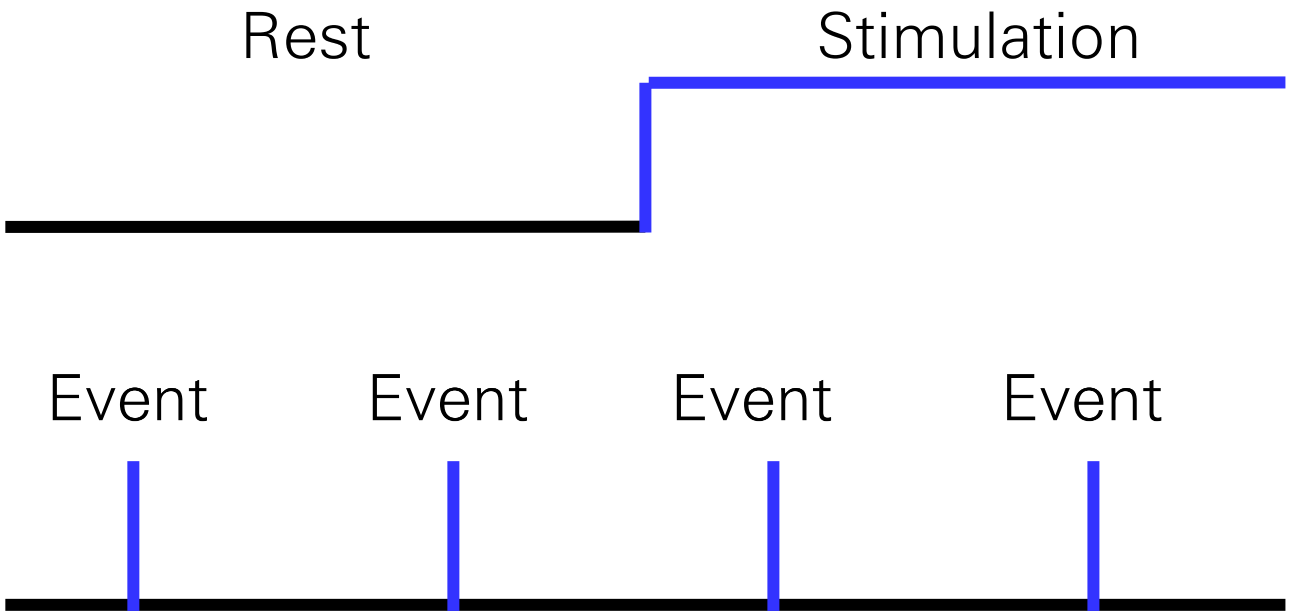
Experimental Designs in fMRI



Experimental Designs in fMRI

Block Design

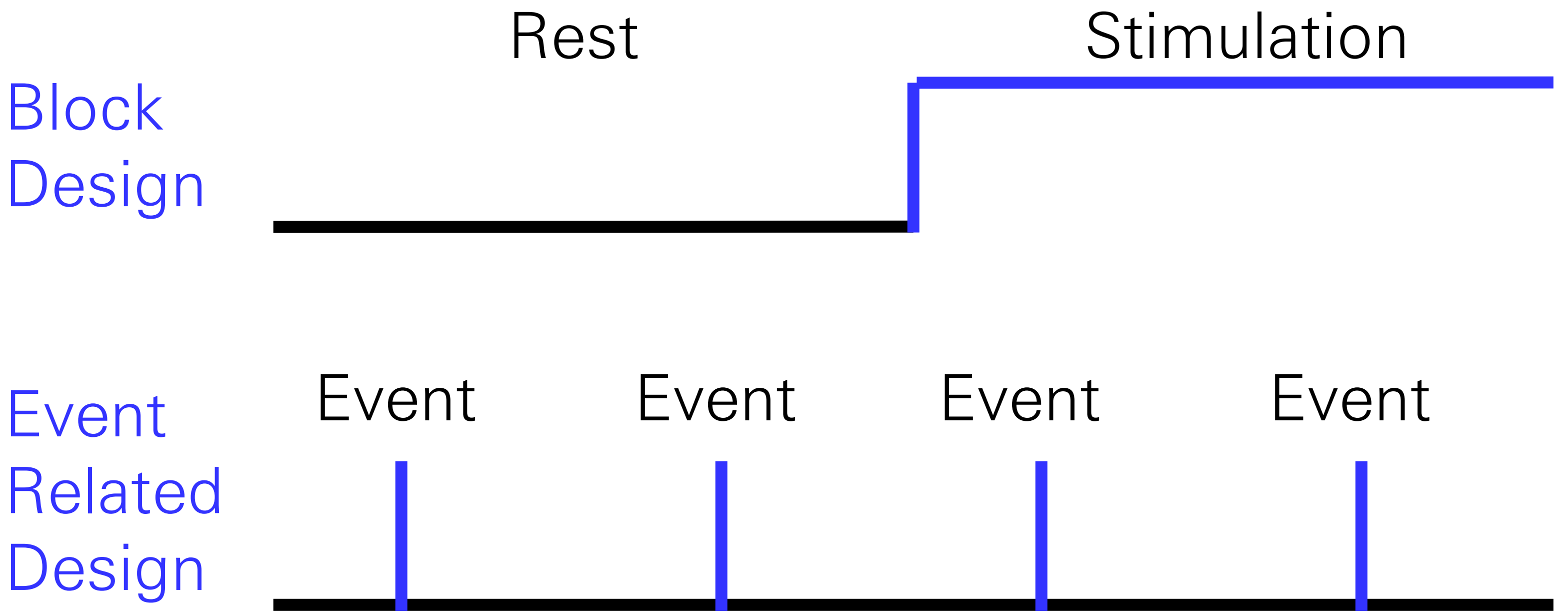
Event Related Design



Implicit assumptions

- Stable baseline or with stochastic fluctuations (noise)
- Stimulation independent of baseline fluctuations

Experimental Designs in fMRI

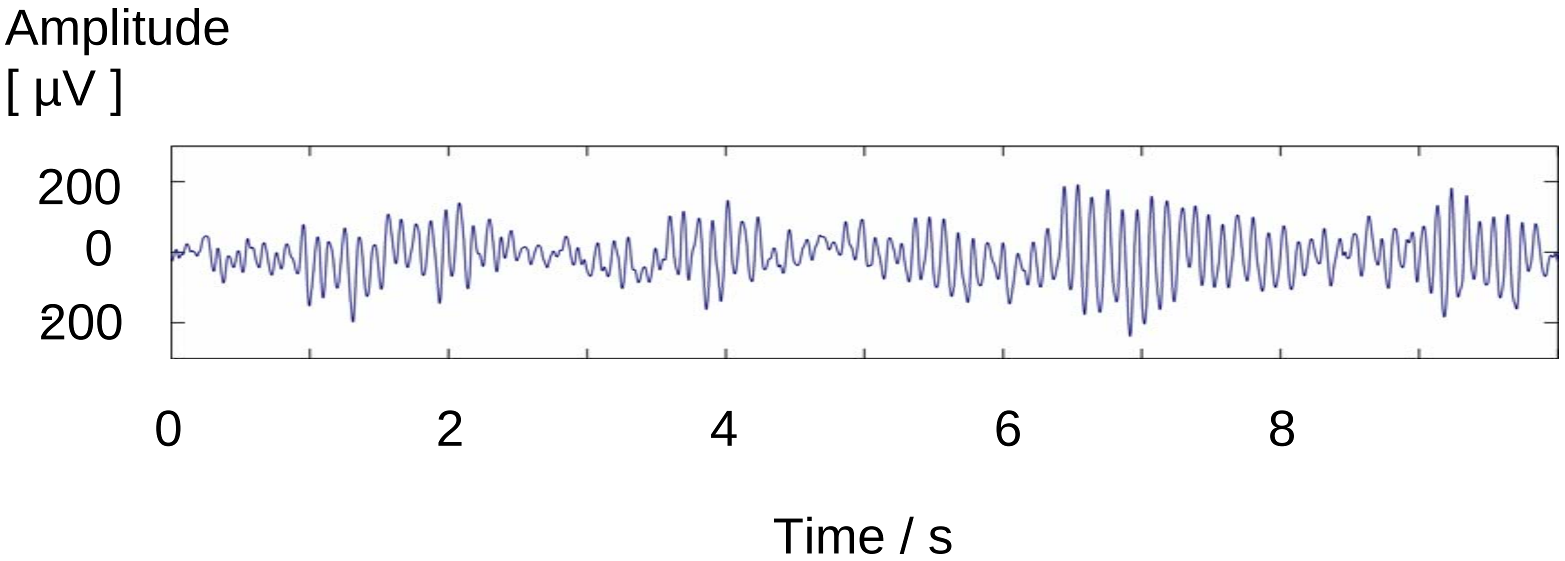


Implicit assumptions

- Stable baseline or with stochastic fluctuations (noise)
- Response to Stimulation independent of baseline fluctuations

Both assumptions wrong/controversial
(Maceig et al. Science 2002)

The “Resting State“ in the Occipital Cortex



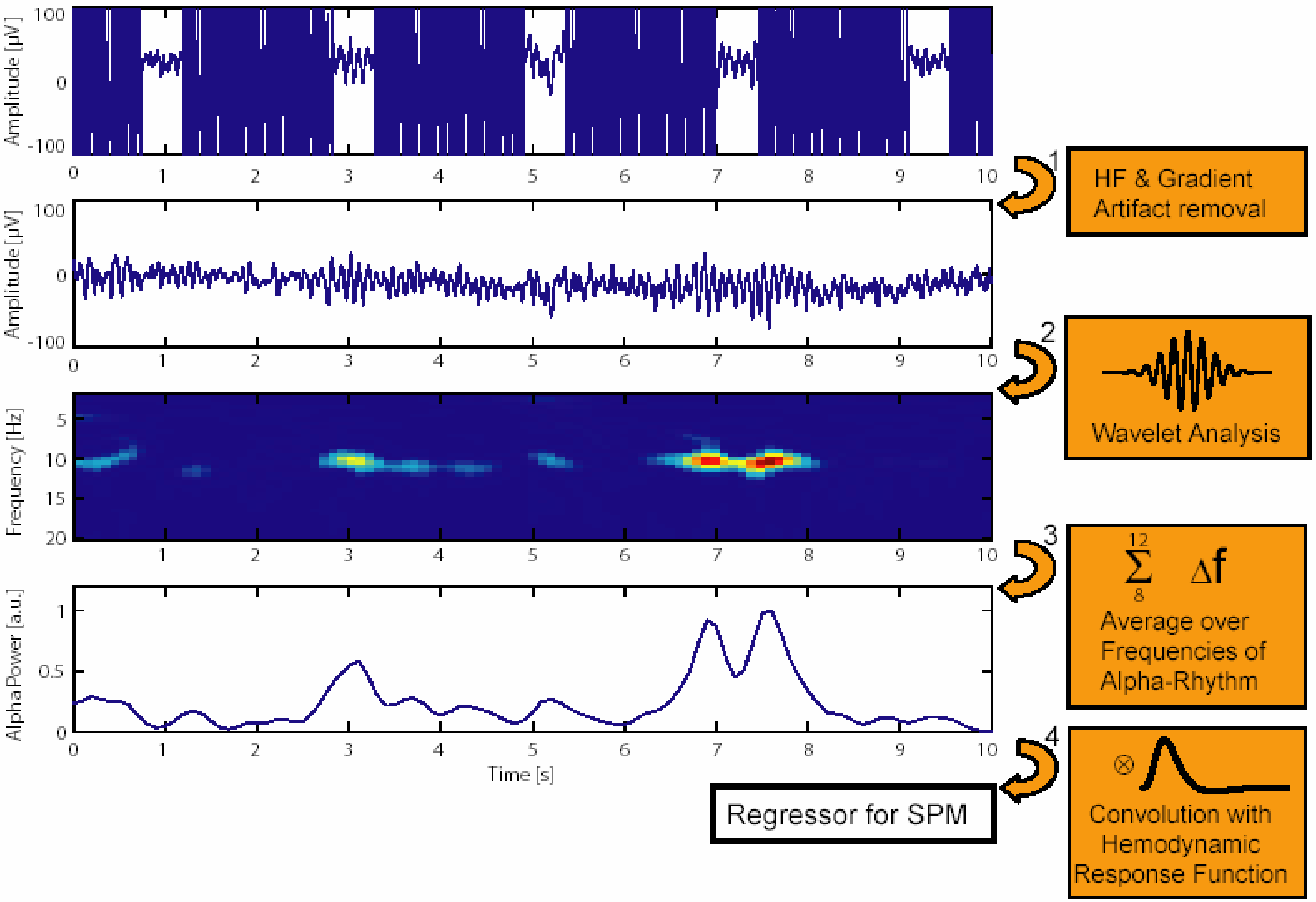
The “Resting State“ in the Occipital Cortex

Are fluctuations of background rhythms

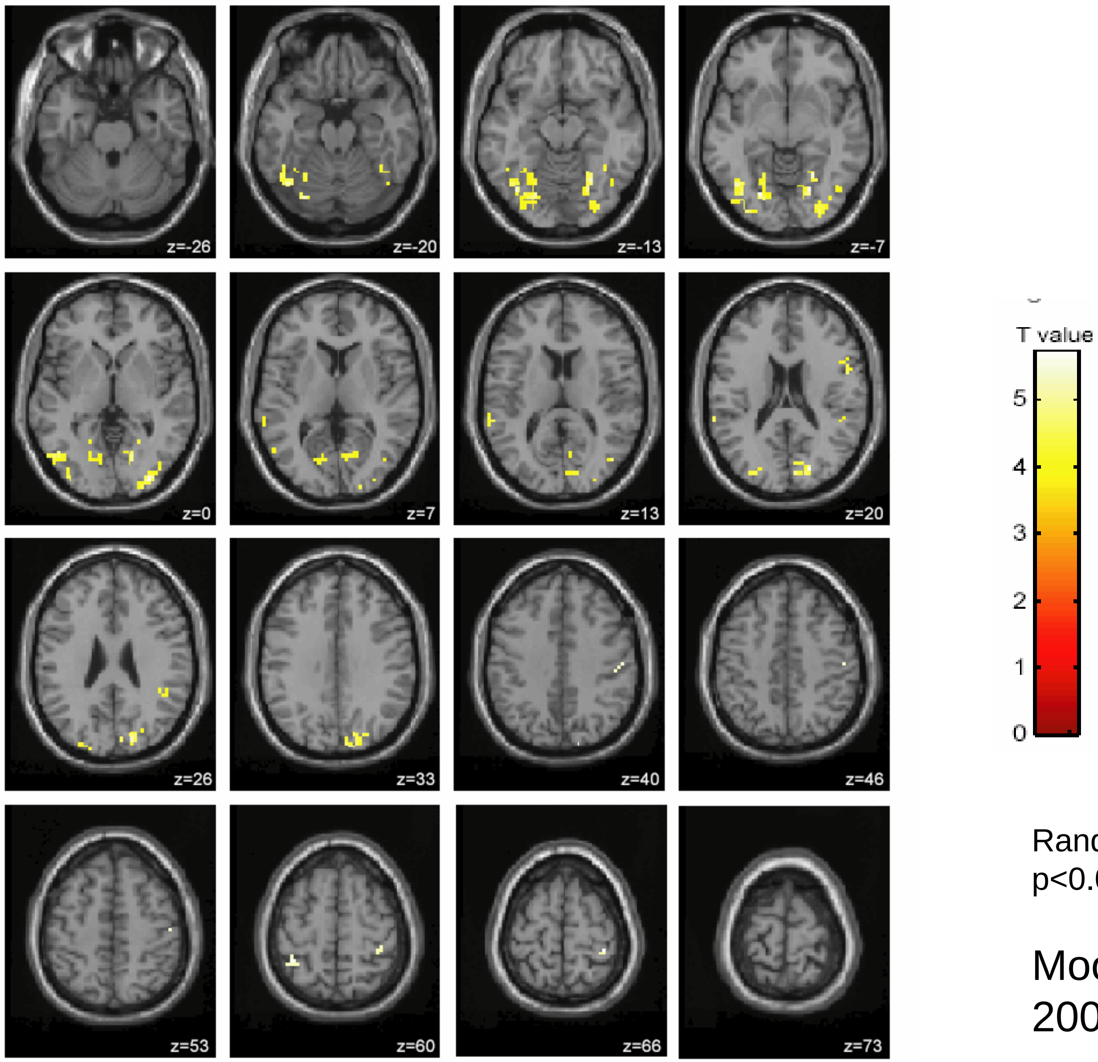
associated with a

vascular (BOLD) response ?

EEG-fMRI Study on BOLD Correlates of Alpha rhythm



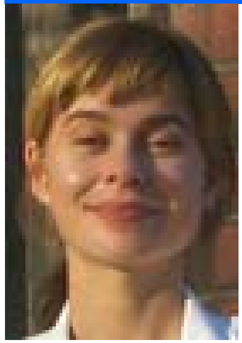
Inverse Correlation of Alpha-Power and BOLD-Signal

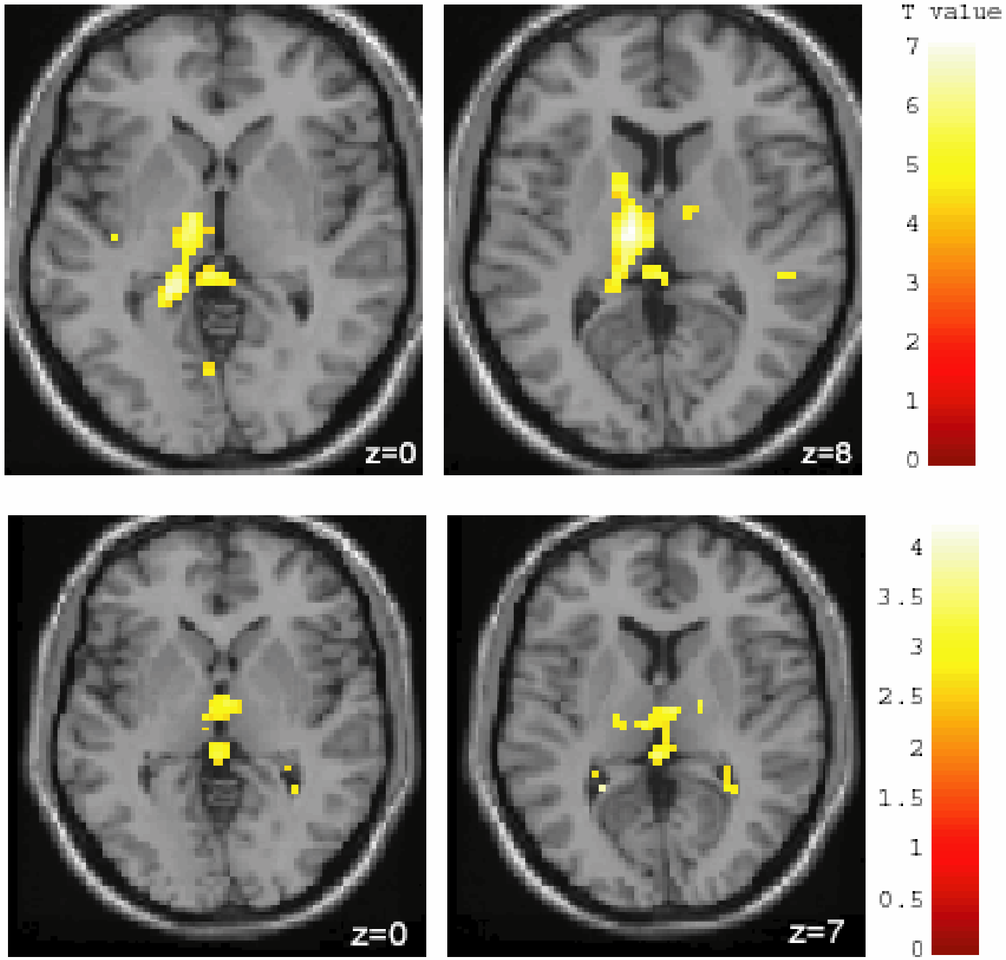


Random effects N=14
$p<0.001$ uncorrected

Moosmann et al.
2003 Neuroimage

POSITIVE correlations of Alpha-Power and BOLD-Signal



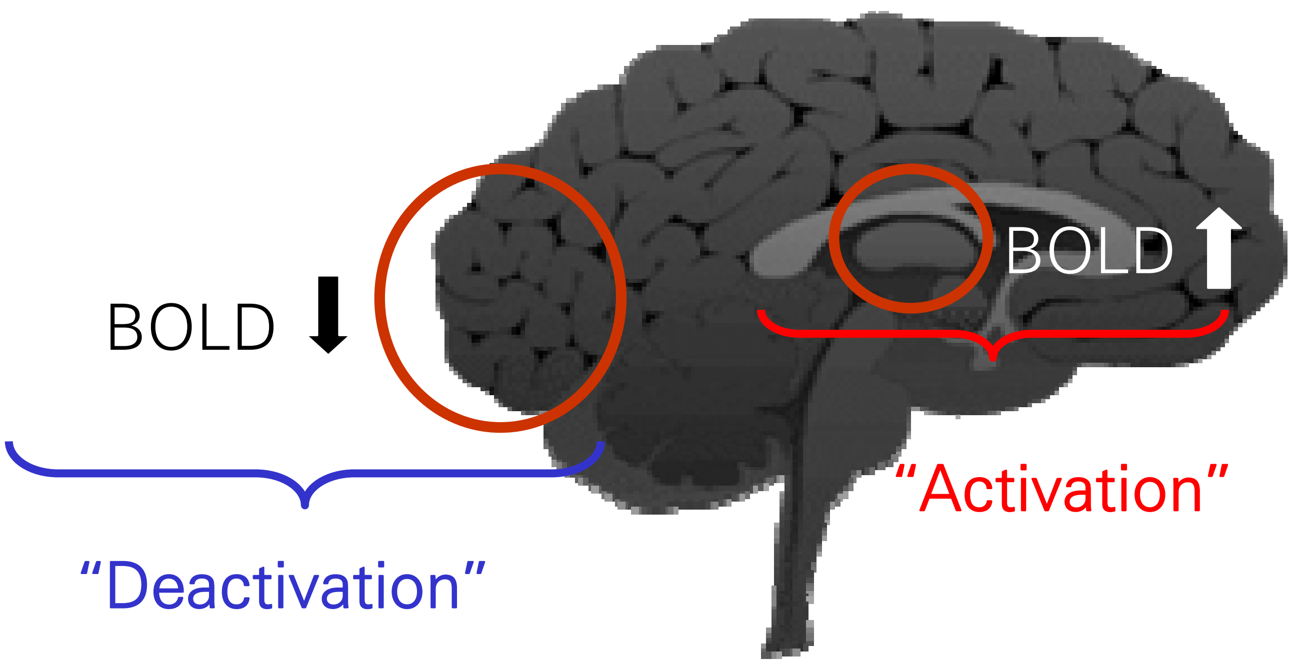


Interleaved EEG-fMRI
Fixed effects N=6
p<0.001 uncorrected

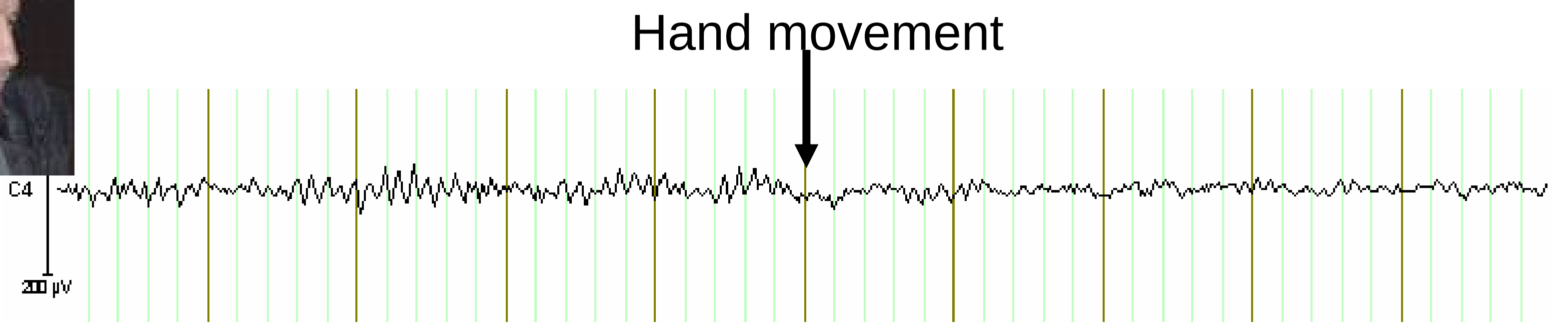
Continuous EEG-fMRI
Random effects N=14
p<0.001 uncorrected

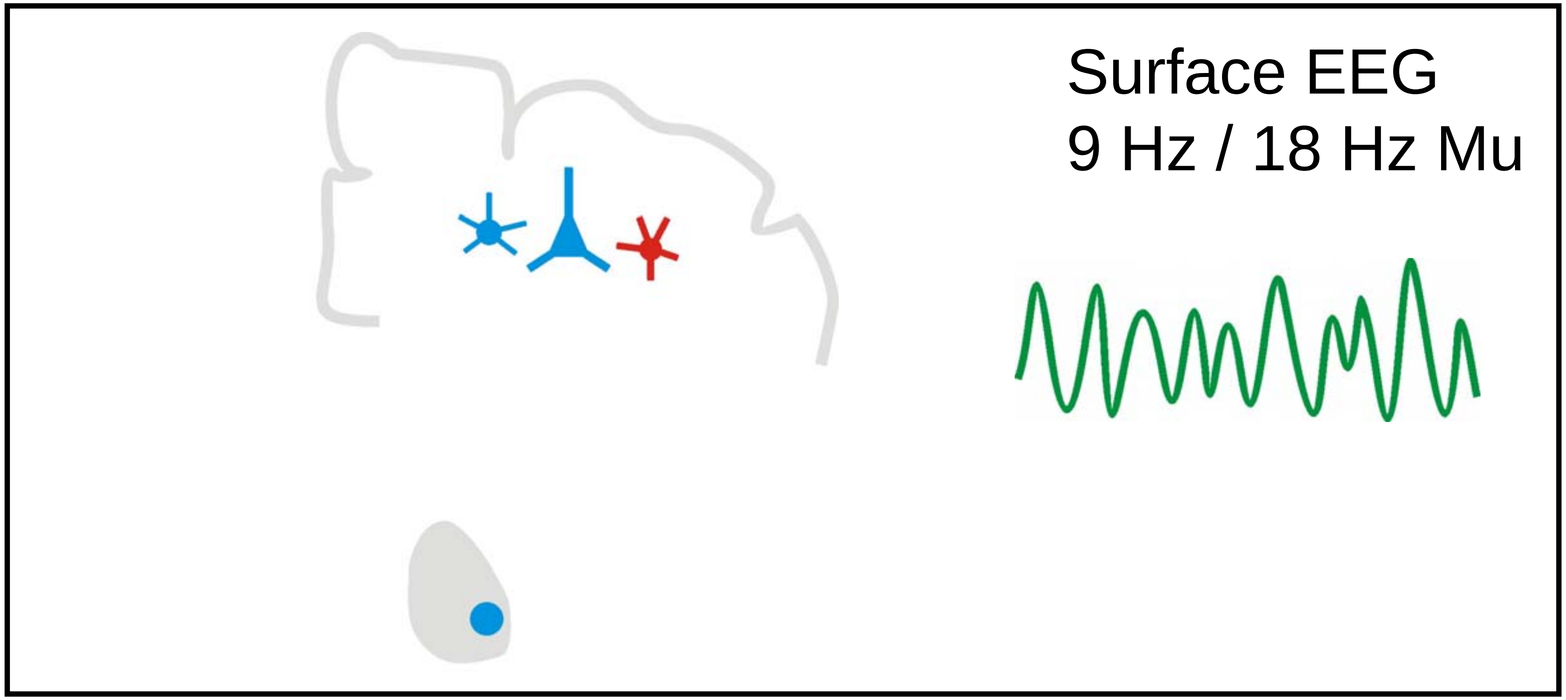
Moosmann et al.
2003 Neuroimage

Model of Alpha Rhythm Generation

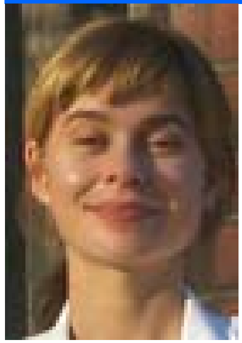


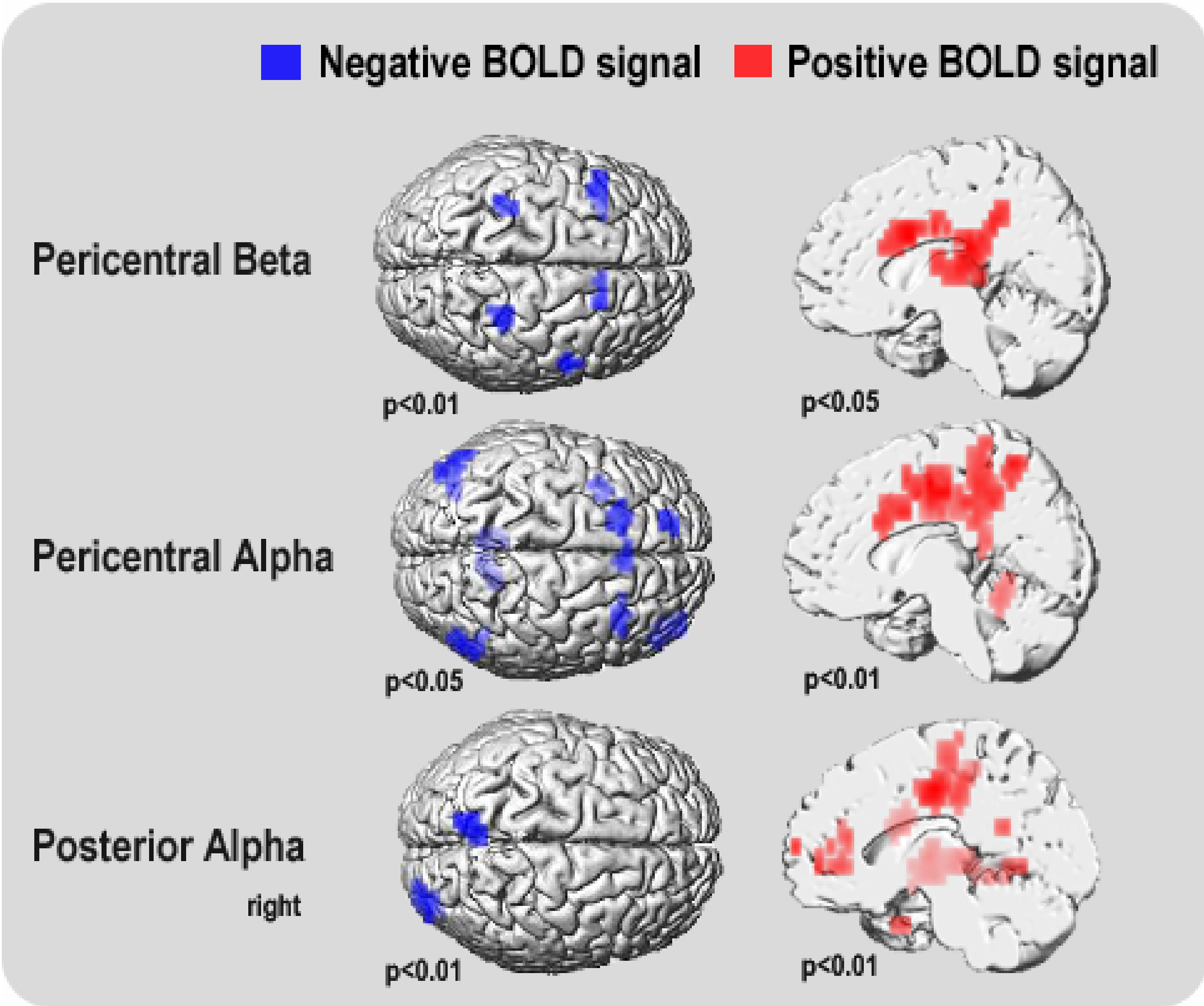
Background Rhythms in Somatomotor System



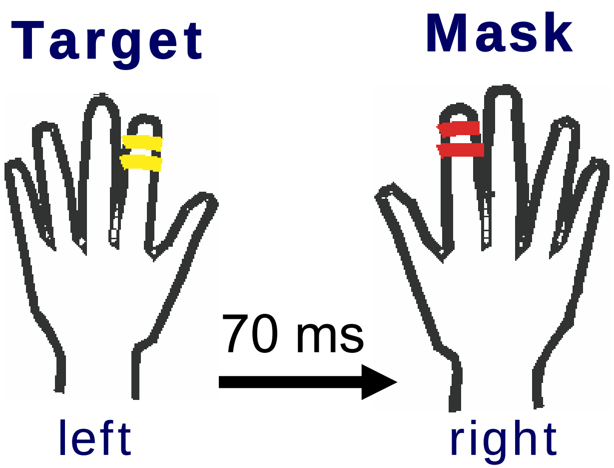


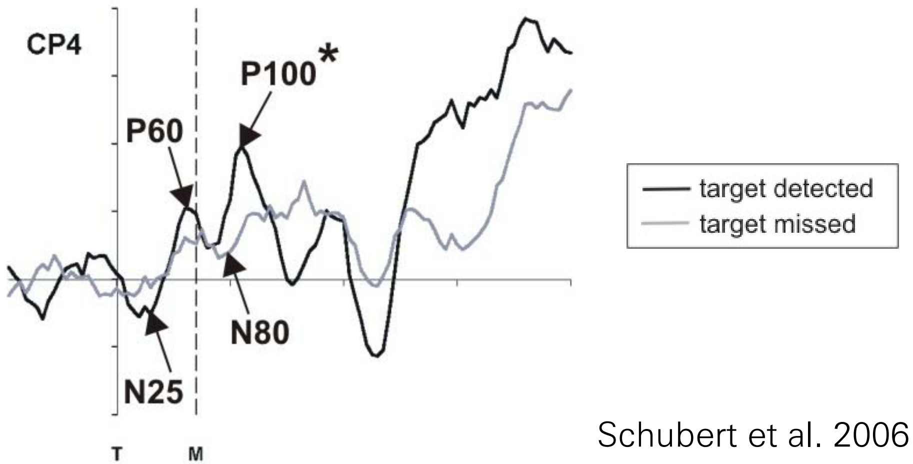
fMRI-Correlates of Different Background Rhythms



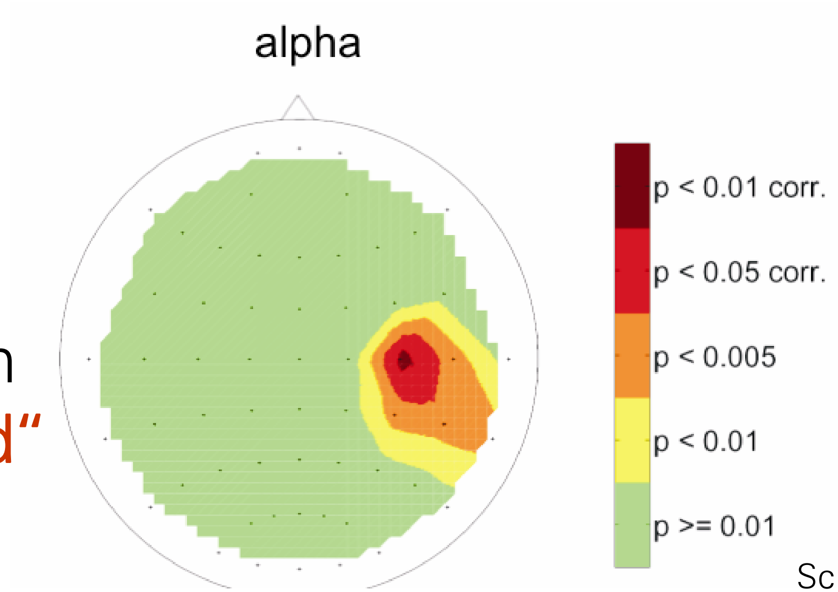


mplitude of Prestimulus Pericentral Alpha Rhythm
etermines Detection of Somatosensory Stimulus





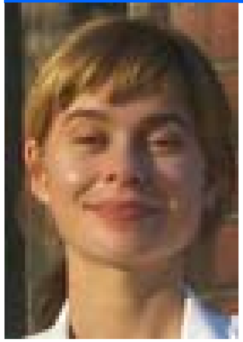
Schubert et al. 2006

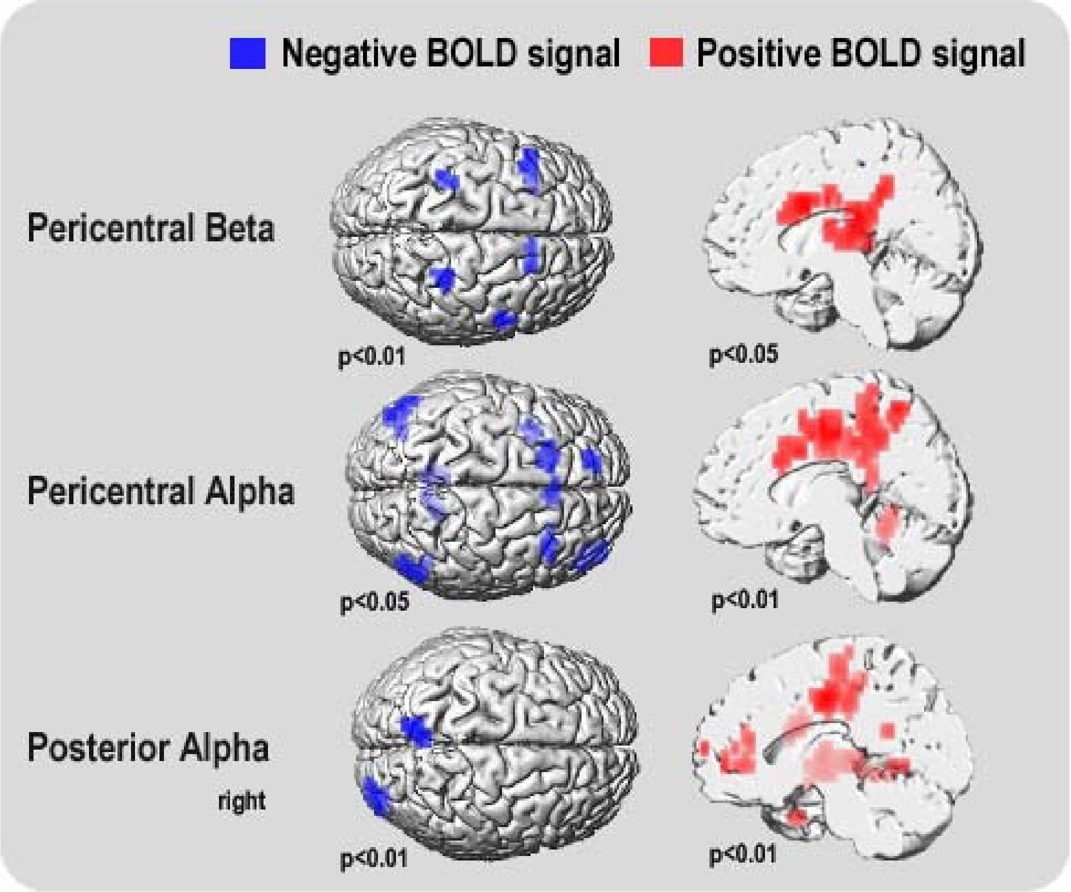


Contrast of Prestimulus
Pericentral Alpha Rhythm
„Missed versus Detected“

Schubert et al. 2007

fMRI-Correlates of Different Background Rhythms





Summary 1: Towards Definition of a Resting State with Functional Imaging

Simultaneous fMRI-EEG allows for assessment of brain areas involved in background rhythms

Pattern emerging for Alpha/Beta idle rhythms :

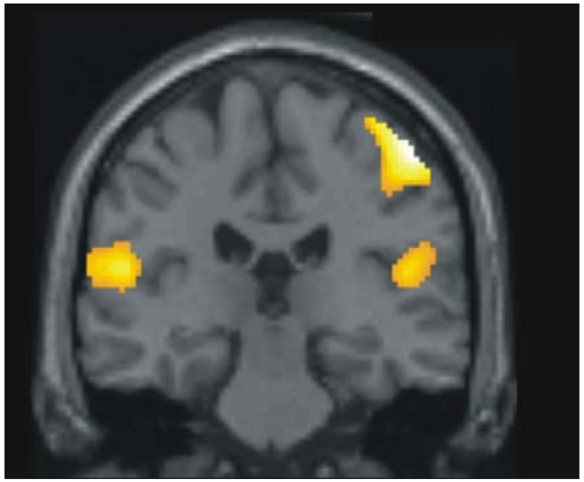
- (Widespread) Cortical "Deactivation"
- Cingular and „Subcortical "Activation"

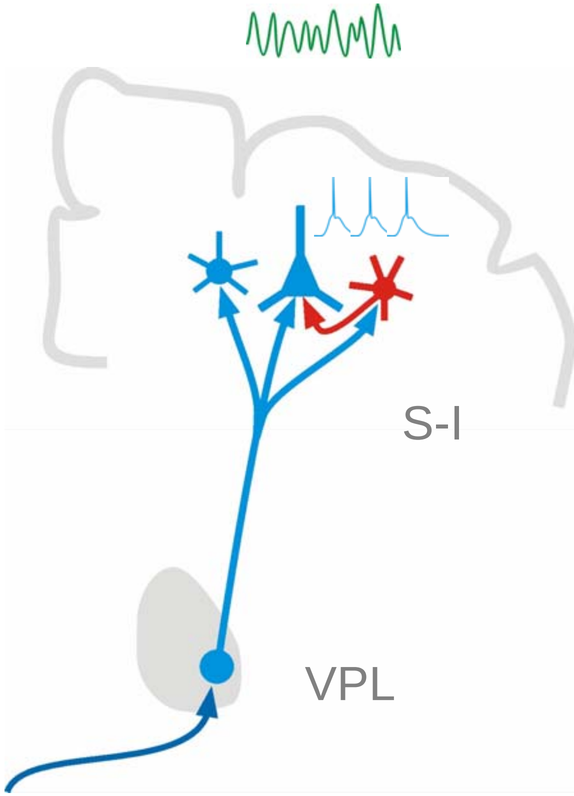
Interaction between background and evoked activity can be addressed (Schubert et al. 2007, Koch et al. J Neurosci 2006)

Open questions

- Involved neurons?
- Other rhythms / types of synchronization?

Neurophysiological Events during Somatosensory Processing





Baseline Activity

Evoked Action Potentials

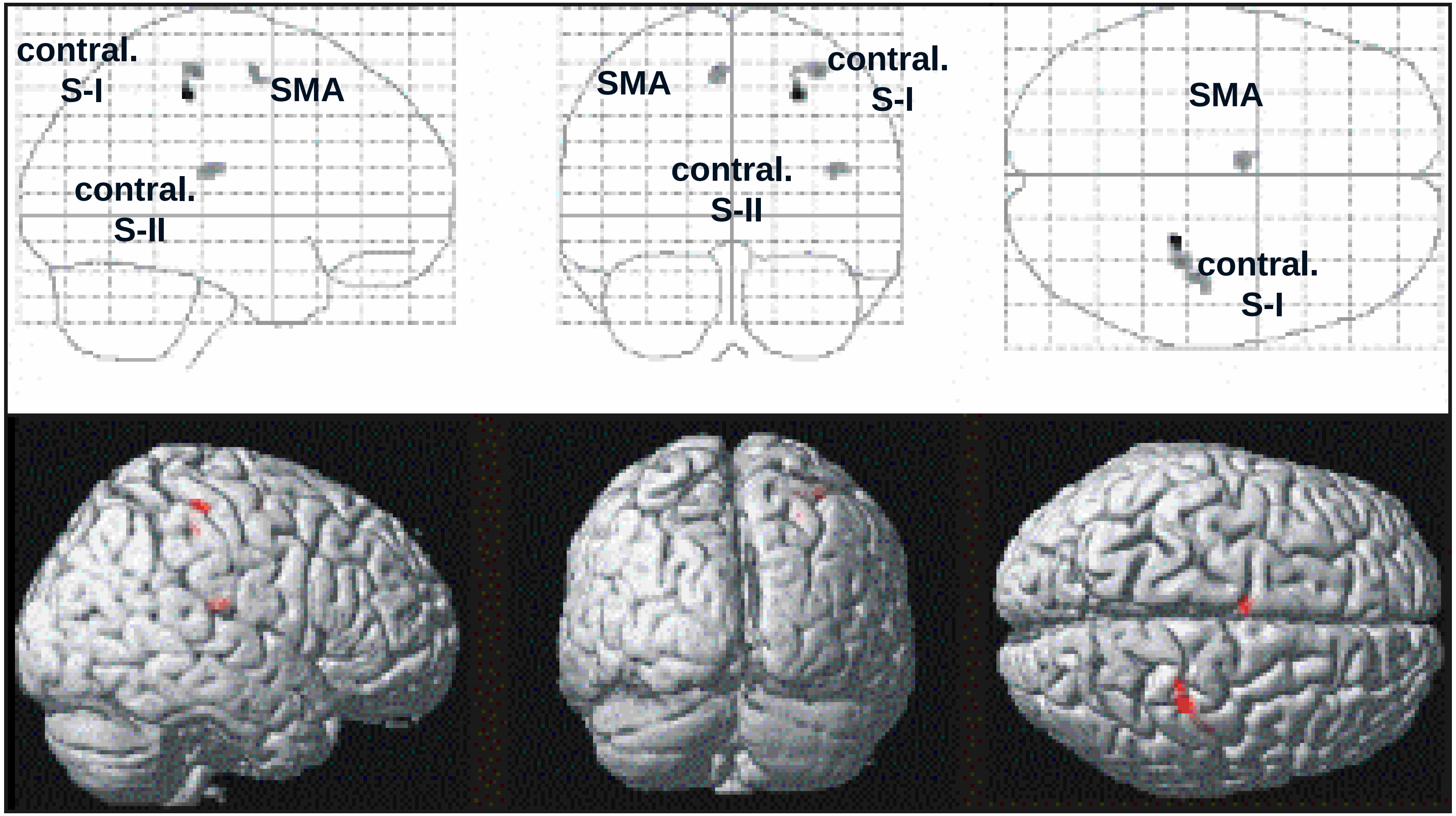
Excitation / Inhibition

How is INHIBITION

reflected in fMRI-BOLD signal?

Negative BOLD during Subliminal Stimulation

($p<10^{-3}$, n=9): contralateral primary, secondary somatosensory cortex, SMA

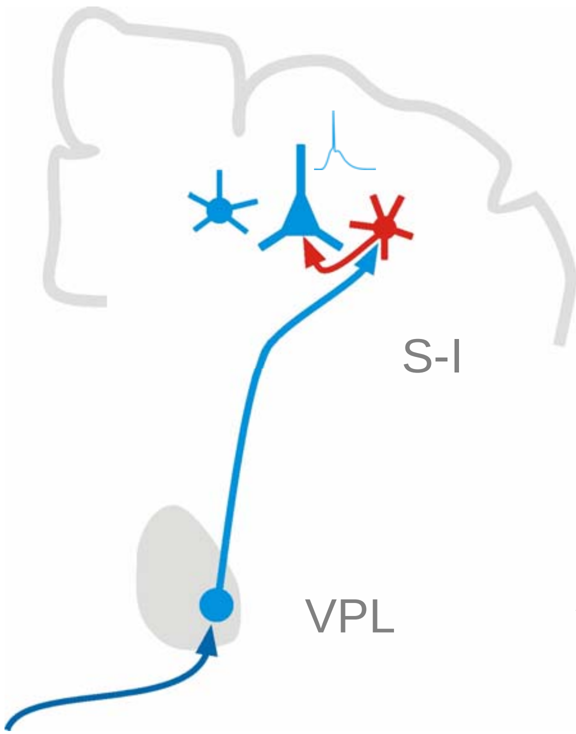


Blankenburg et al. Science 2003

Model of Inhibition ?

At low stimulation intensity inhibitory interneurons are preferentially activated

Feed forward Inhibition



Swadlow et al. 1999

Inhibition and BOLD-fMRI

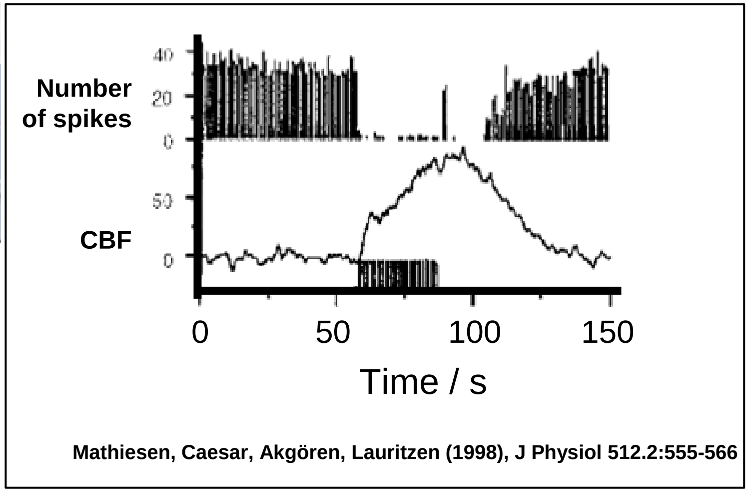
Does INHIBITION

of the output neuron

(via local interneurons)

always lead to a DEACTIVATION in fMRI?

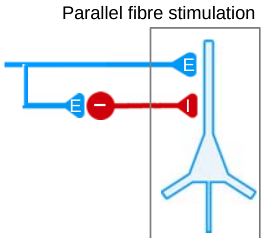
Inhibition and BOLD-fMRI



Does INHIBITION

of the output neuron

(via local interneurons)



always lead to a DEACTIVATION in fMRI?

Inhibition and BOLD-fMRI

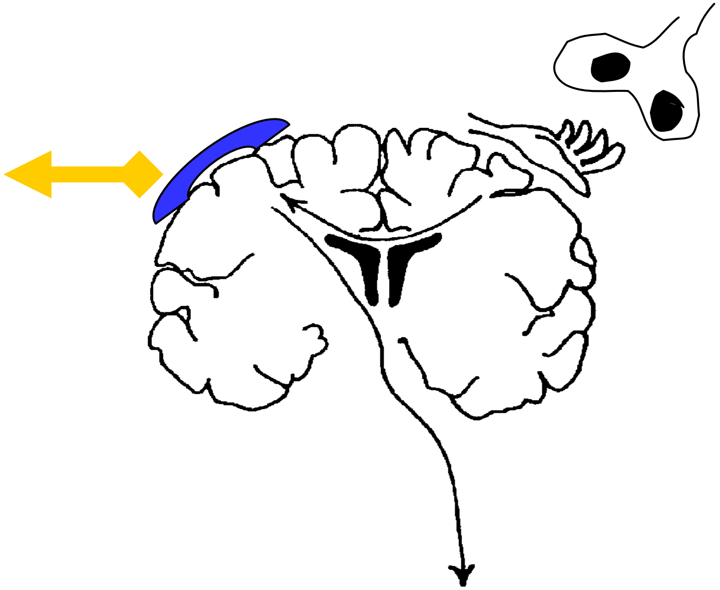
Does INHIBITION

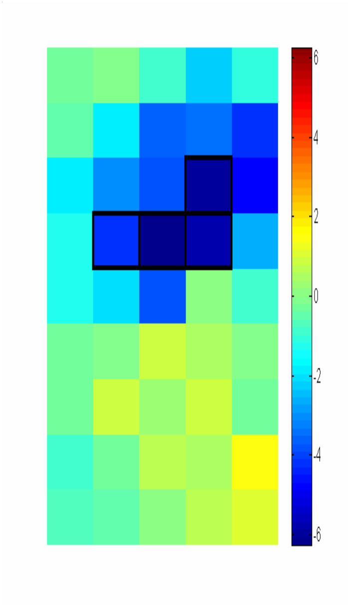
of the output neuron

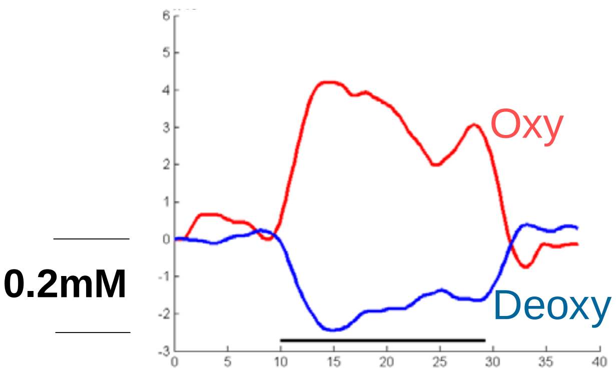
(via local interneurons)

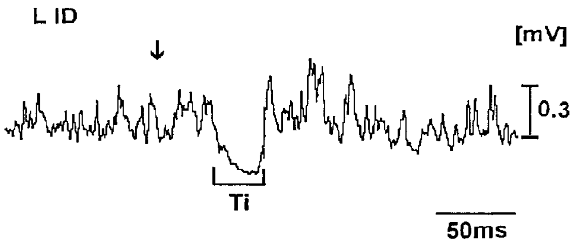
always lead to a DEACTIVATION in fMRI?

Effect of transcallosal Inhibition (TI) on local Hb-Oxygenation?





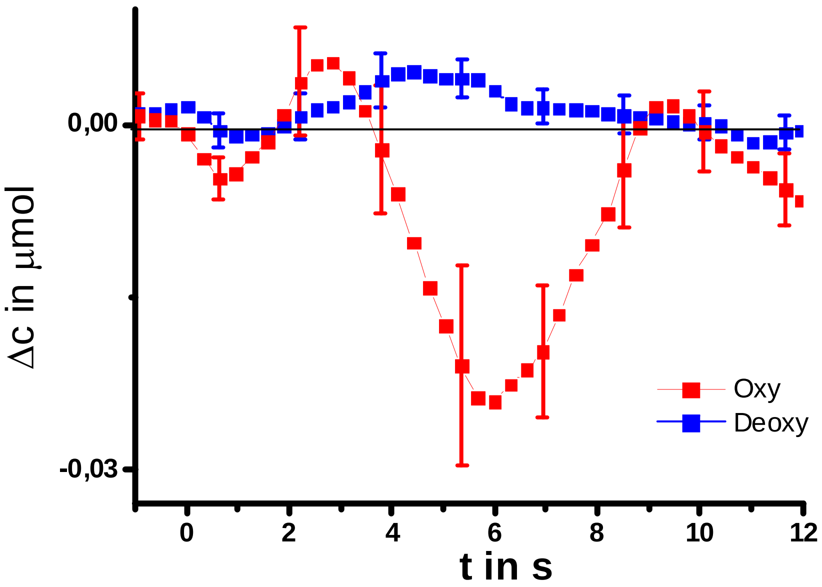




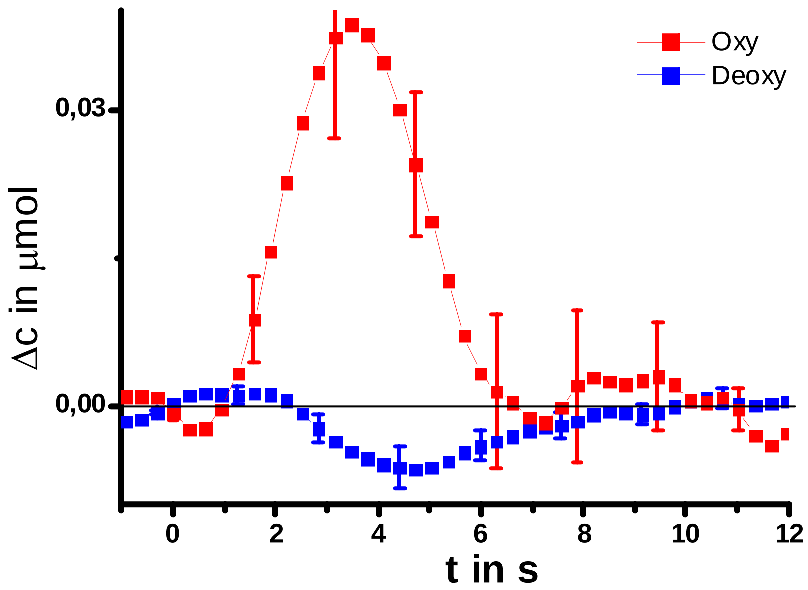
IPSI-lateral muscle

Effect of TI on Cortex
Depends on Baseline Condition

Effect of TI with Pre-innervation



Effect of TI without Pre-innervation



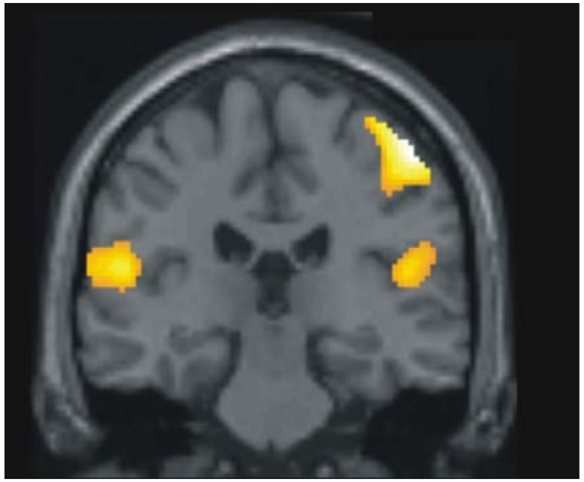
Summary 2: Inhibition in fMRI

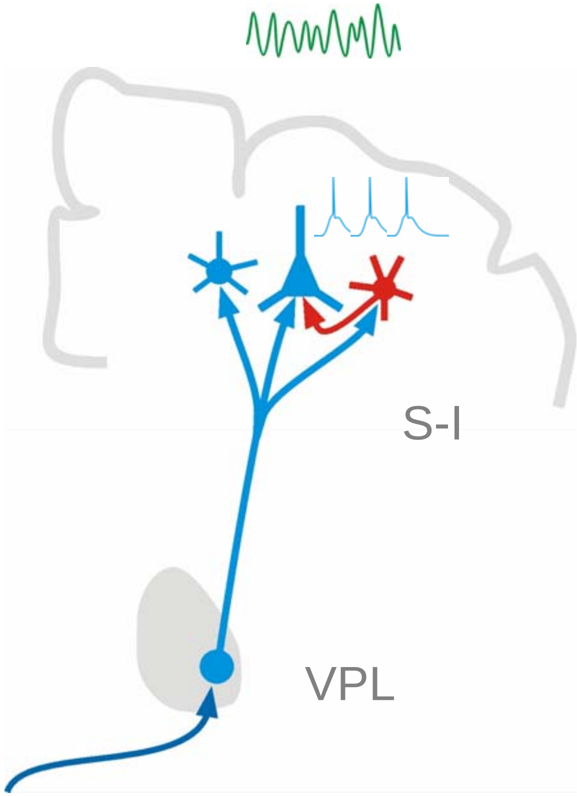
The effect of inhibition on fMRI signal is context-sensitive

Most likely due to two competing effects:
- Inhibition „per se“:
  Increased metabolism / fMRI signal

- Inhibition-induced reduction of local activity:
  Decreased metabolism / fMRI signal

Neurophysiological Events during Somatosensory Processing



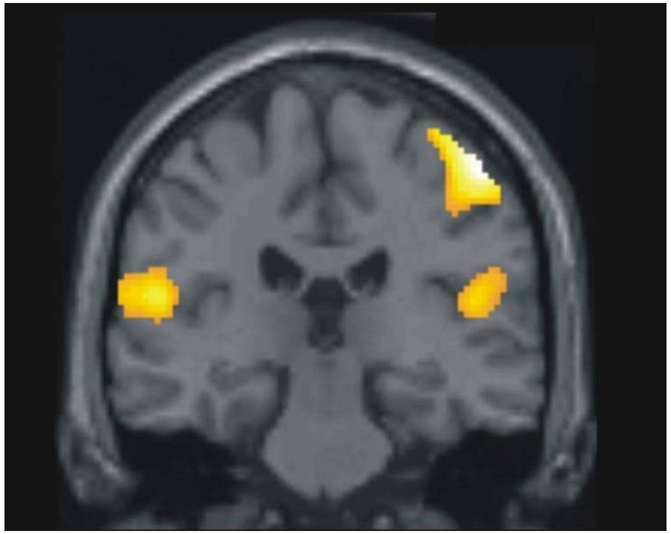


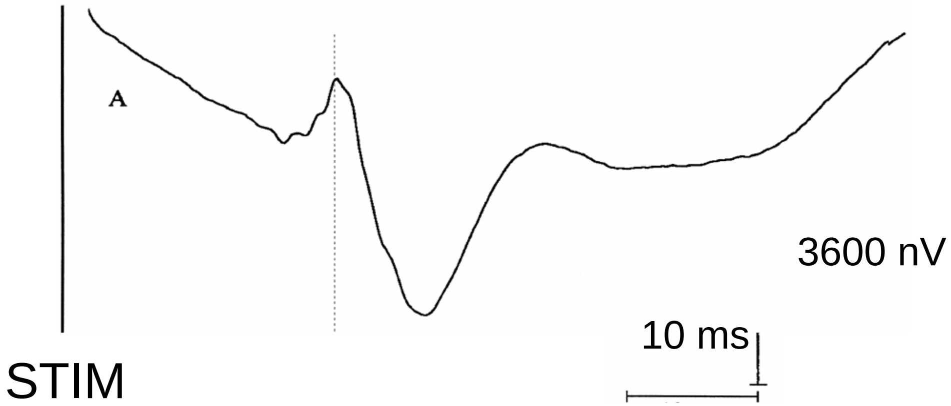
Baseline Activity

Evoked Action Potentials

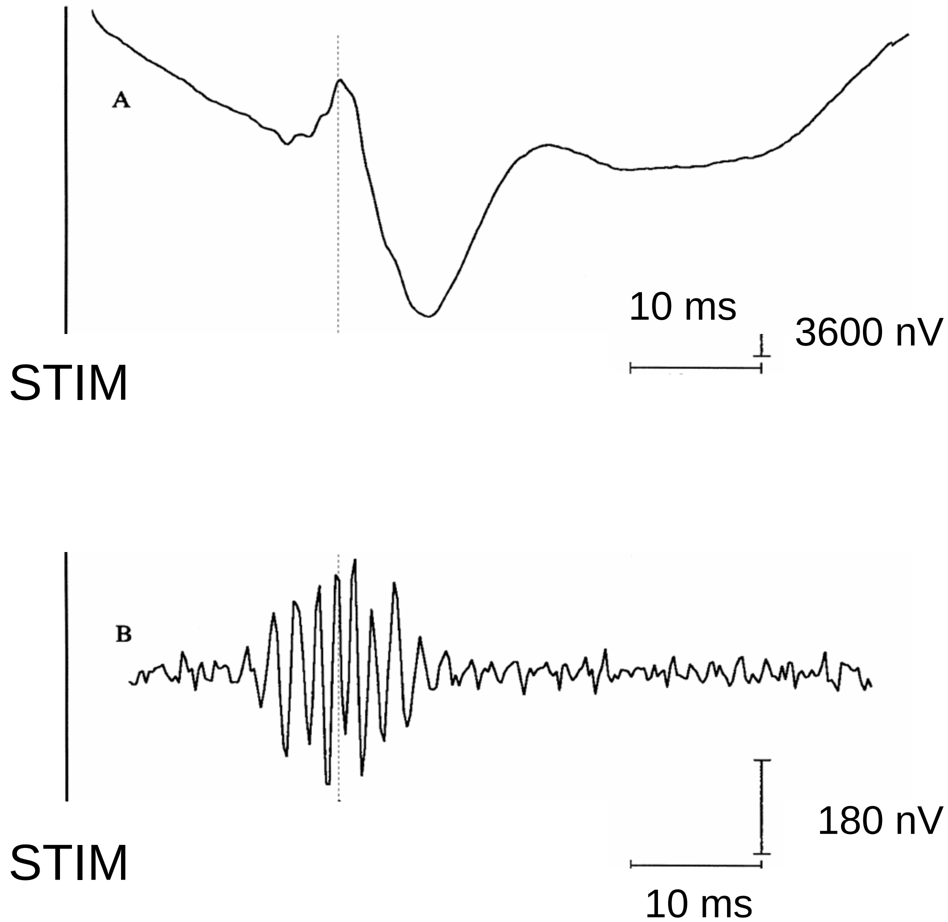
Excitation / Inhibition

Combining
fMRI with Measurement of Evoked Potentials



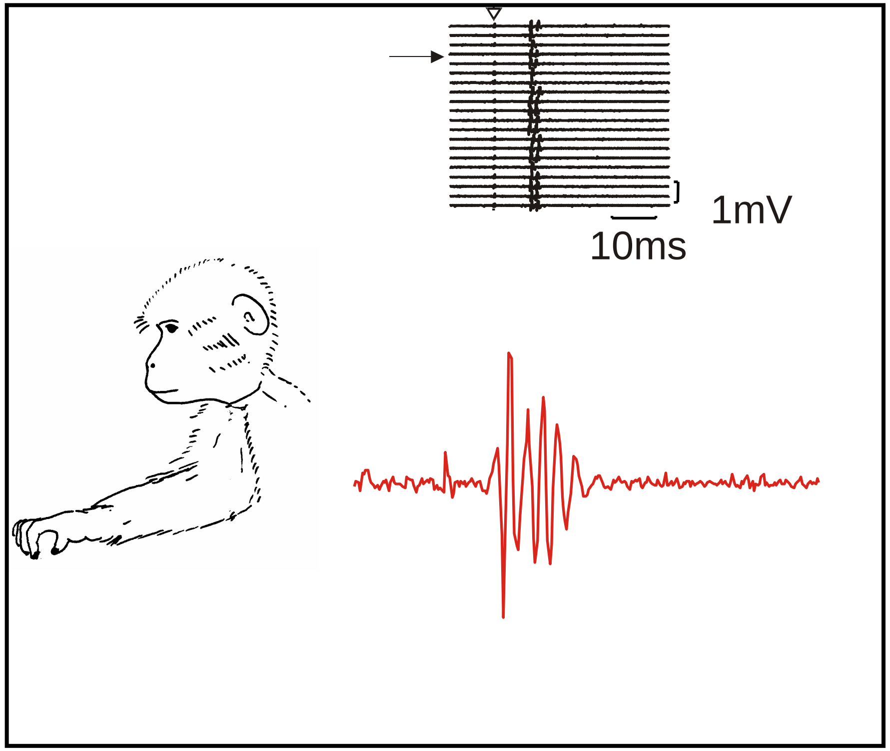


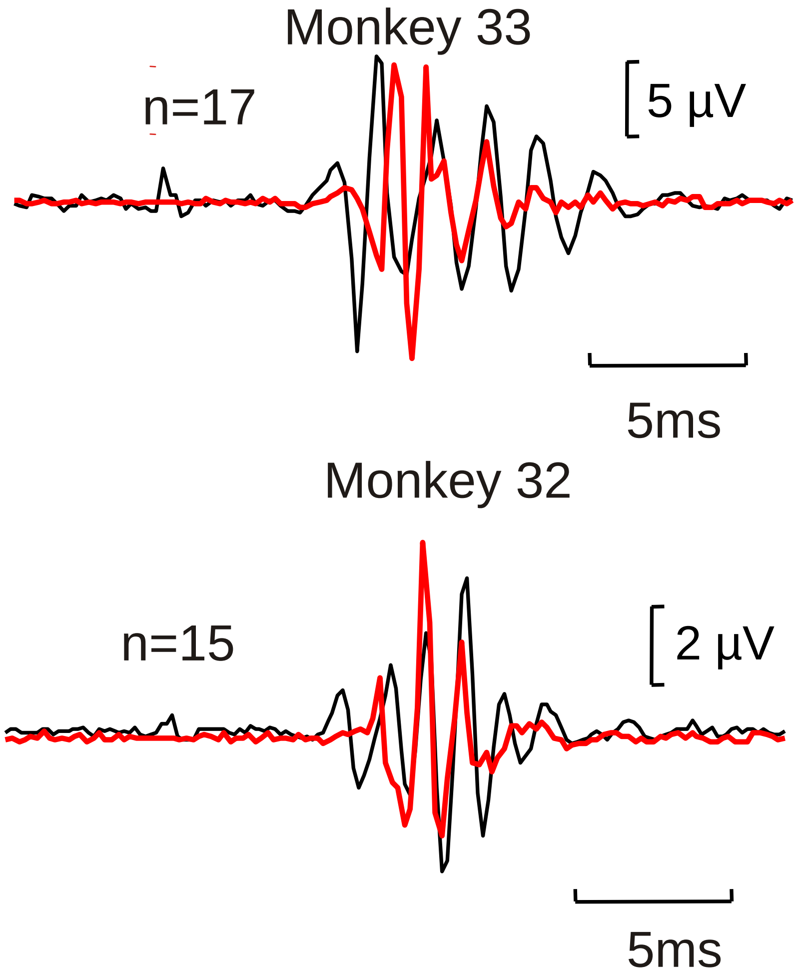
High-Frequency (600 Hz) Oscillations during Somatosensory Stimulation



Curio et al. 1994, 1997, 2000
Hashimoto et al. 1996, 2000

Late HFO Component Correspond to Cortical Spike Bursts

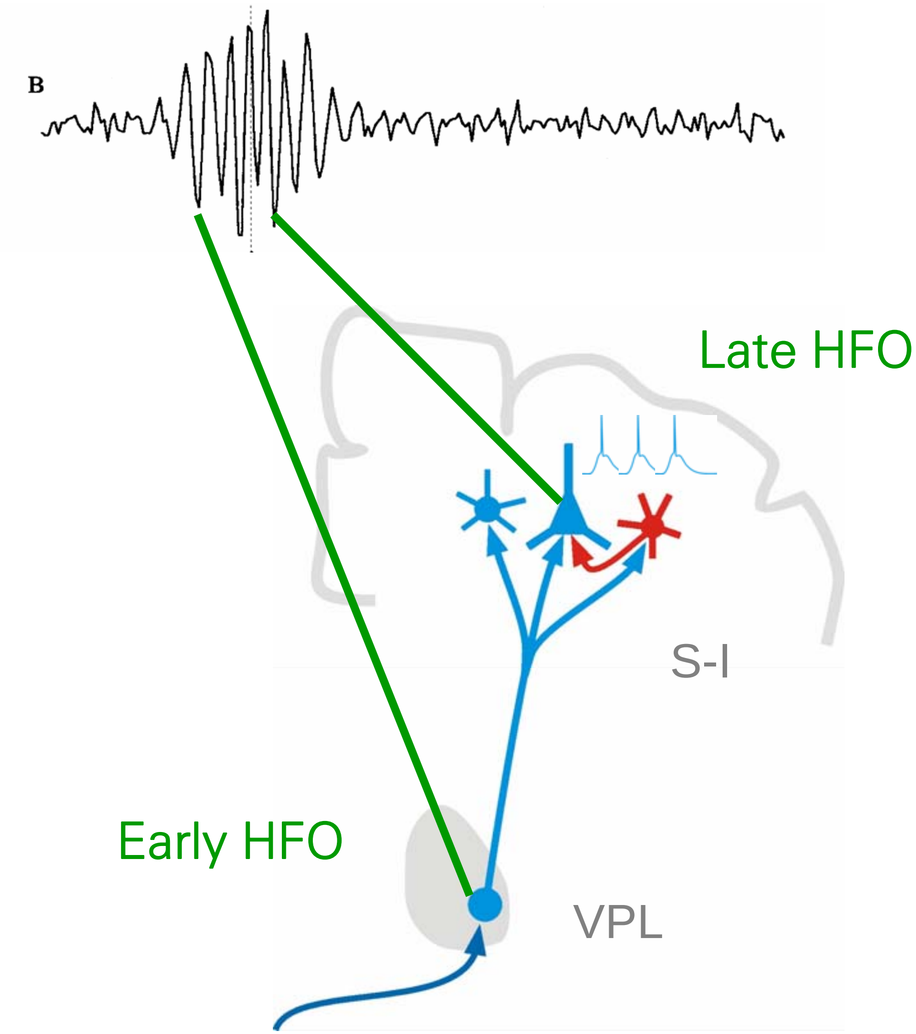


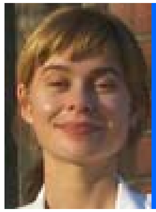


epidural EEG
summed single unit PSTHs

(Baker, Curio, Lemon J. Physiol. 2003

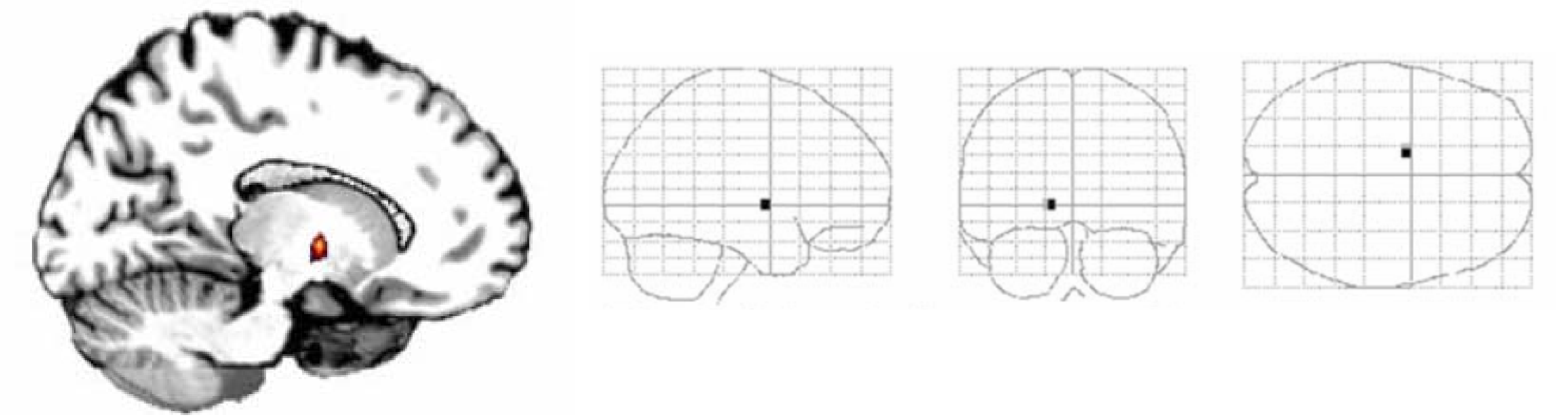
Early and Late HFO Represent Presynaptic AP and Cortical Spike Bursts



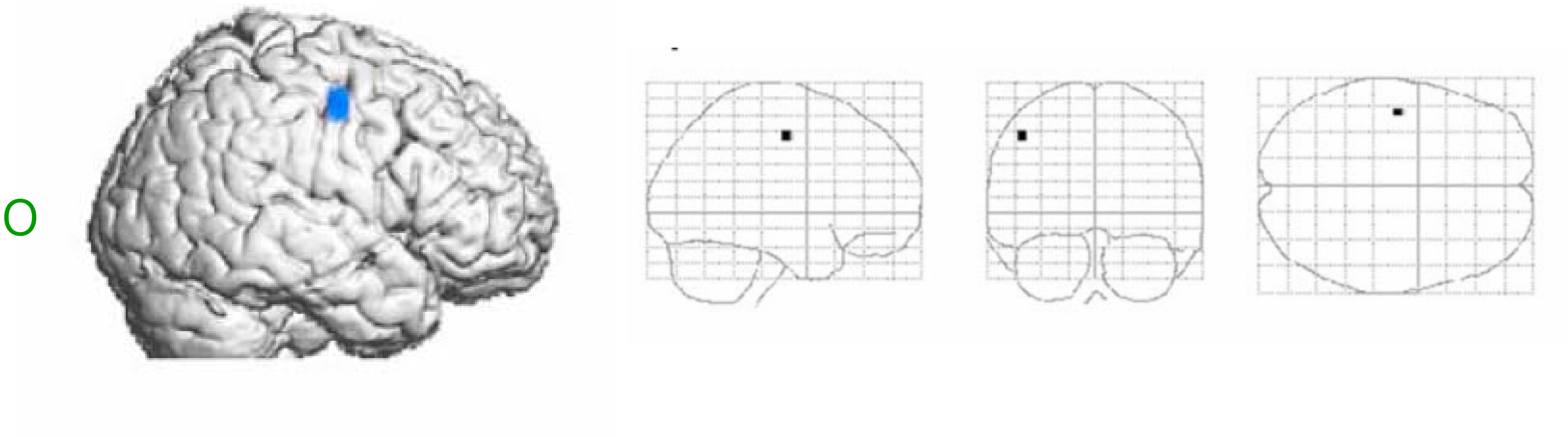


Correlates of Early and Late Parts of HFO

Early HFO



Late HFO



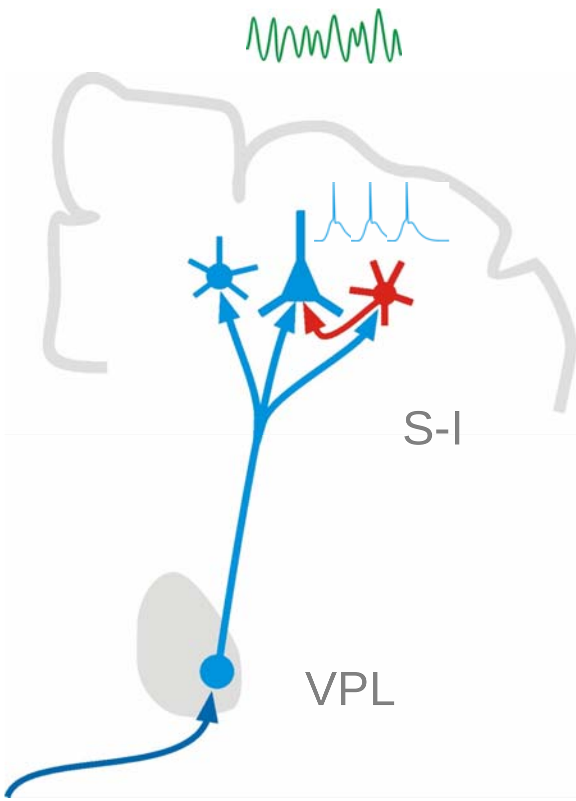
Summary 3 : Spike Burst and fMRI

High Frequency EEG-oscillations (HFO, spike bursts) can be recovered from simultaneous EEG-fMRI studies.

Modulation of HFO is associated with distinct BOLD correlates:

Early HFO	Contralateral Thalamus
Late HFO	Contralateral S1

Neurophysiological Events during Somatosensory Processing



Baseline Activity

Evoked Action Potentials

Excitation / Inhibition

Danke

Berlin NeuroImaging Center
BNIC

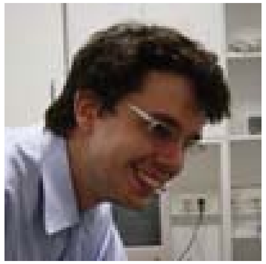
Hellmuth Obrig

Robert Becker

Felix Blankenburg

Gabriel Curio

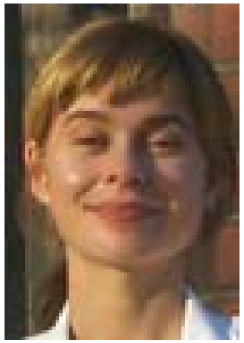
Rüdiger Wenzel



Jens Steinbrink

Matthias Moosmann

Isabell Wartenburger



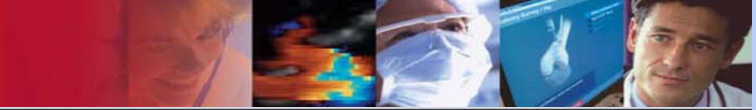
Petra Ritter

Frank Freyer

Birol Taskin

Ruth Schubert

ALEXIAN ADVANCED MEDICINE



Alexian Neurosciences Institute

Multimodal Noninvasive Brain Imaging for Guiding Neurosurgical Interventions: Integration of MEG, fMRI, and MRS

Jeffrey David Lewine, Ph.D.

Diretor, Illinois MEG Center

Director, Alexian Brothers Center for Brain Research,

Elk Grove Village, IL

ALEXIAN BROTHERS

HOSPITAL NETWORK

Alexian Brothers Medical Center

St. Alexius Medical Center

Alexian Brothers Behavioral Health Hospital

Alexian Rehabilitation Hospital

The Problem

- In order to achieve the best possible outcomes for their patients, surgeons treating brain tumors or epilepsy must maximize the removal of diseased or dysfunctional tissue while simultaneously preserving the integrity of healthy tissue supporting critical functions. This requires detailed and interactive information on the location and spatial extent of the tissue to be removed, plus information on the spatial organization of the brain with respect to eloquent cortical areas.

The Solution

- Noninvasive brain imaging methods can significantly simplify the surgical planning process.

- Three of the most promising methods are
  - magnetoencephalography (MEG)
  - functional MRI (fMRI)
  - MR spectroscopy (MRS)

- Each method has advantages and disadvantages depending on the question in hand, and in many cases, data from multiple methods need to be integrated to provide a complete roadmap for surgical planning.

Mapping Eloquent Cortex

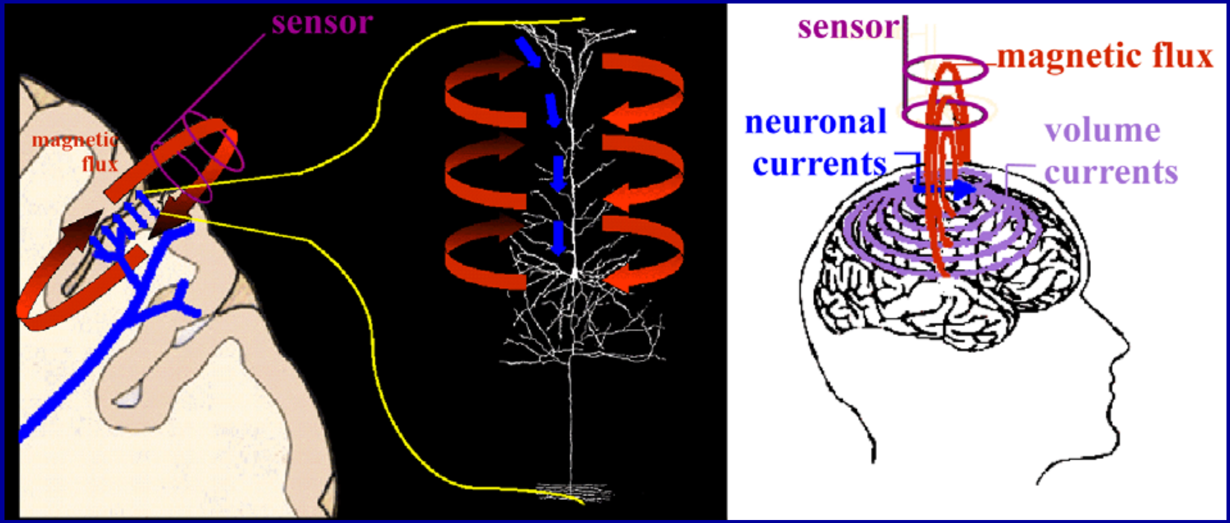
- In considering eloquent cortical regions, mapping of sensorimotor and language regions are generally considered to be the most important. MEG and fMRI are the two most promising noninvasive methods for these applications.

- MEG directly measures the magnetic fields generated by the brain's electrical activity. Using source modeling strategies it is possible to track brain activity patterns in both space and time.

- fMRI takes advantage of the differential magnetic properties of oxygenated and deoxygenated blood. When a brain region is active there is generally an increase in the supply of oxygenated blood to the region. Whereas the spatial resolution of fMRI is quite good, its temporal resolution is debated. Also, blood-based effects are tertiary to electrophysiological activity and disease processes may alter the coupling between changes in brain activity and changes in bloodflow.

How Does MEG Work?

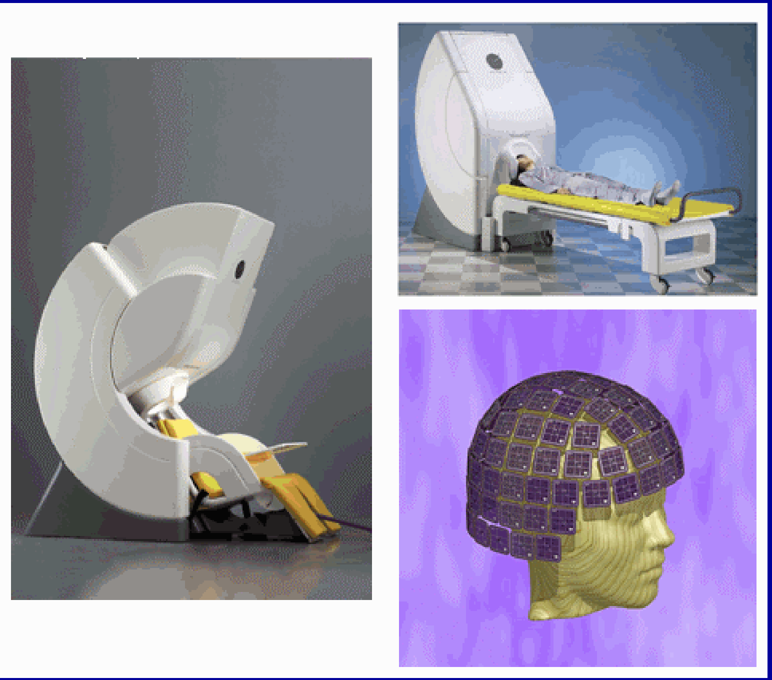
- All time-varying currents have a surrounding magnetic field.



How does MEG work?

- Changes in magnetic flux can be measured using special super-cooled sensors coupled to SQUIDs. Typically, the magnetic field pattern is recorded using a helmet shaped array containing hundreds of sensors

- MEG can be used to measure background brain activity or responses evoked by specific sensory, motor, or cognitive events.



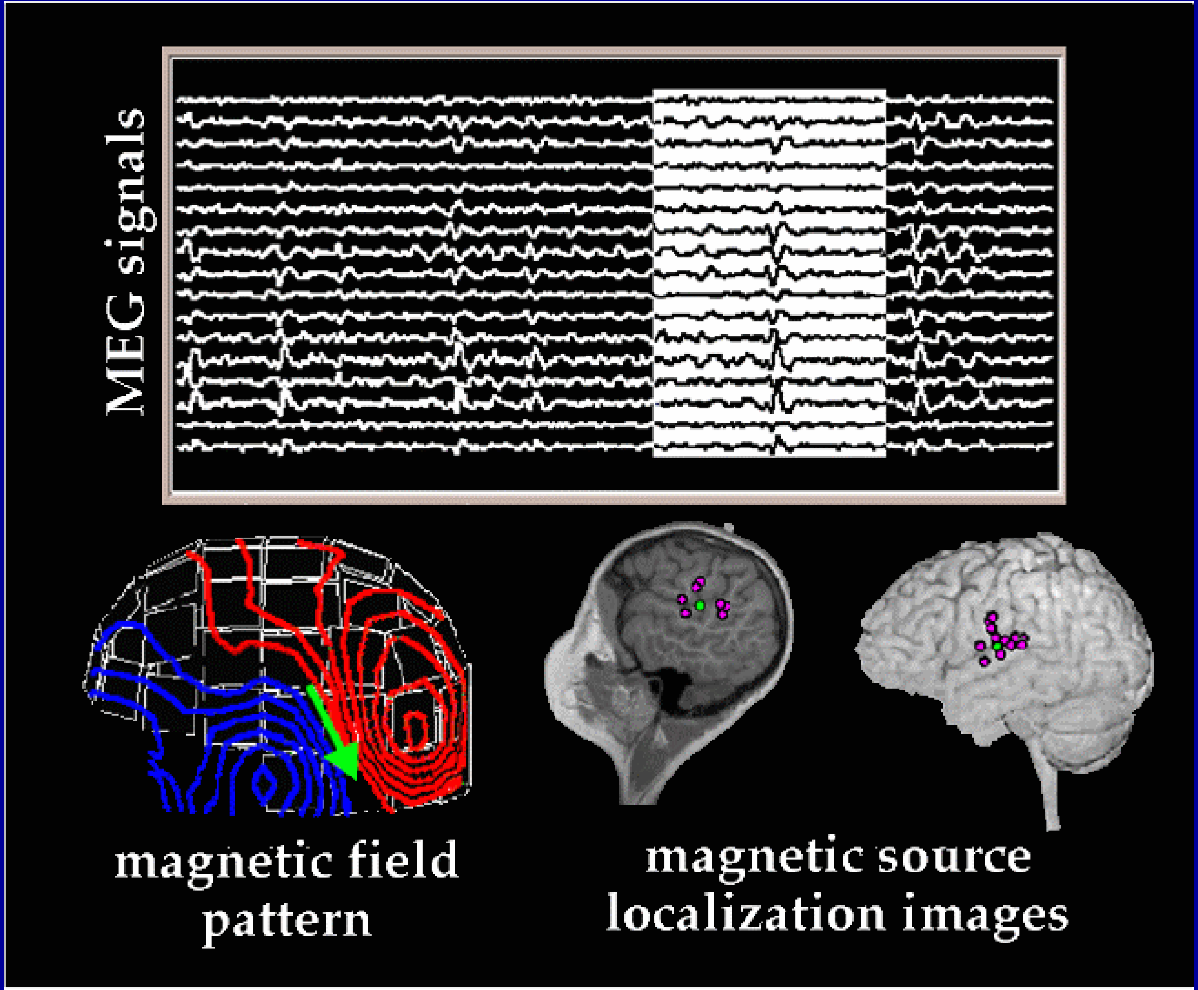
What Can Be Evaluated Using MEG?

- MEG evaluations focus on either spontaneous or evoked data.
- Spontaneous data may be visually inspected for identification of epileptic spike or sharpwaves, and for focal and diffuse slow-waves, with source modeling then used to identify implicated brain regions.
- Spontaneous data can also be subjected to spectral analyses that focus on the amplitude and distribution of background brain rhythms [e.g., delta, theta, alpha, beta, and gamma activity] and patterns of coherence [a measure of functional connectivity] within and between brain regions.
- Using signal averaging techniques, evoked magnetic fields [like EEG related evoked potentials] can be generated. These are useful for examining functional organization of the brain and tracking patterns of activity associated with motor, sensory, and/or cognitive processing.

How Does MEG Work?

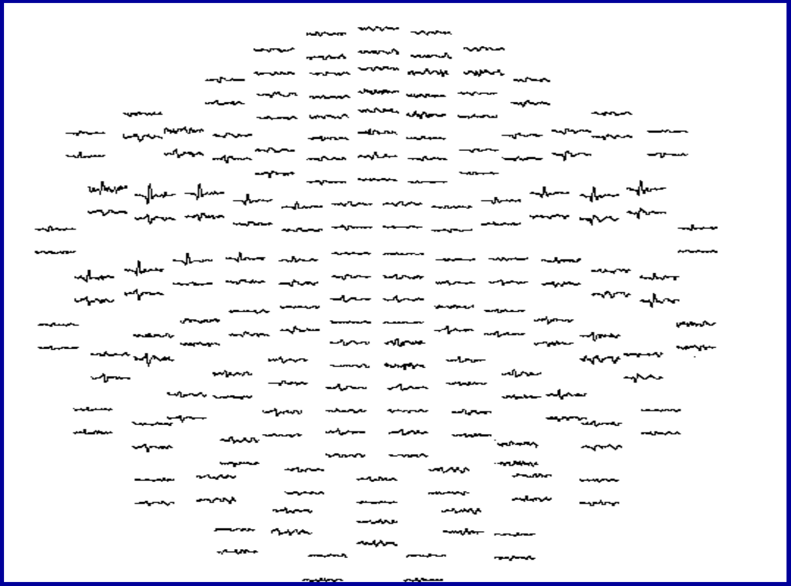
The output of each sensor is a time-varying waveform showing the magnitude of the local magnetic flux.

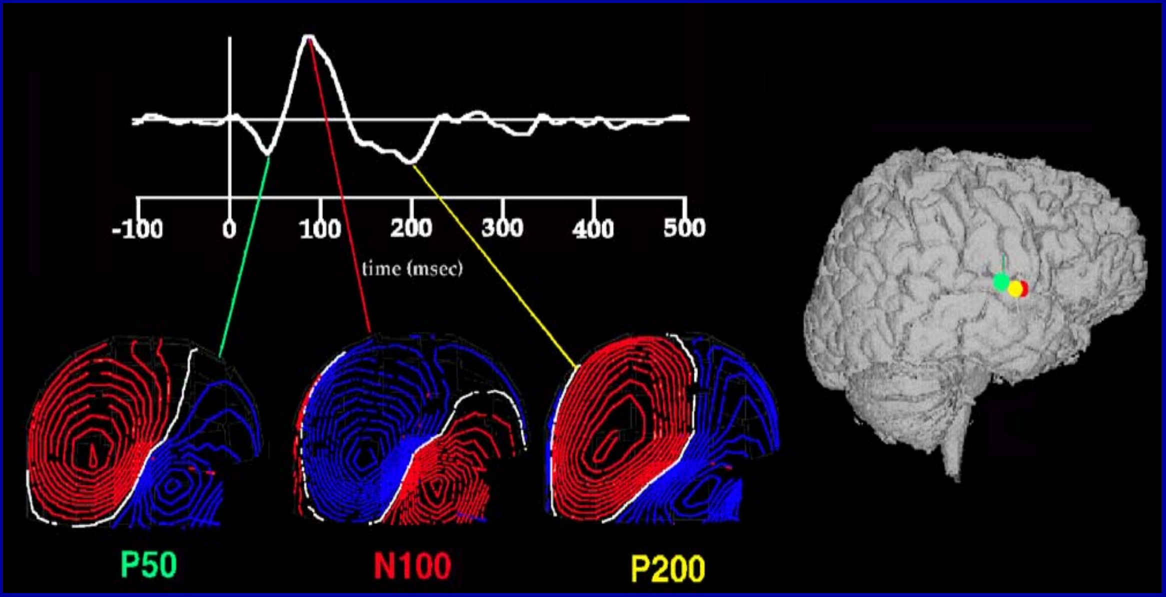
Through assessment of the pattern of magnetic activity, inferences can be made on the location of sources for signal components on interest. MEG source information ca be plotted on spatially aligned MR images to generate magnetic source localization images.



MEG Examines Brain Organization

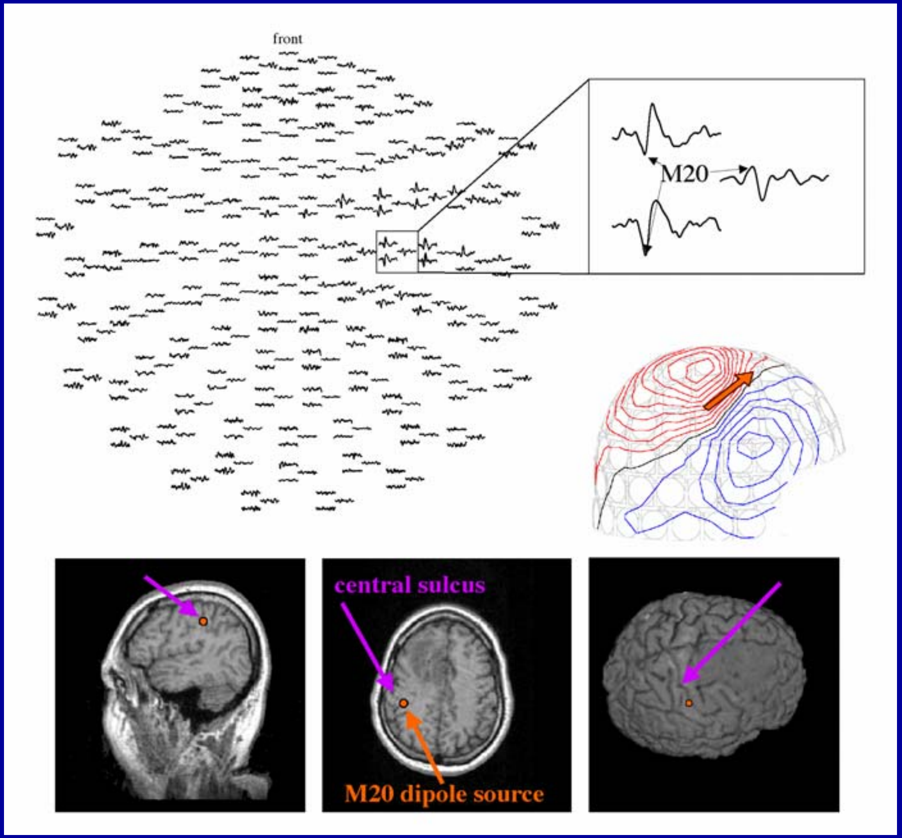
- MEG is used to track information processing in both space and time. Data were collected in response to repeat presentation of a 1000 Hz tone. The sensor map shows auditory evoked responses over right and left lateral sensors located over the temporal lobes. The magnetic field pattern over each hemisphere changes in time. Data are shown over the right hemisphere where first the area in green, then the area in red, and then the area in yellow are activated in sequence.





MEG is used to examine brain organization for the purpose of pre-surgical planning

- MEG provides for efficient presurgical mapping of somatosensory, auditory, visual, and motor function, and identification of cerebral dominance for language.



Examples of Somatosensory Mapping and Identification of the Central Sulcus

Lewine et al, 2007, submitted

- MEG sensorimotor mapping in 120 patients, with tumor or AVM in frontal or parietal lobe.

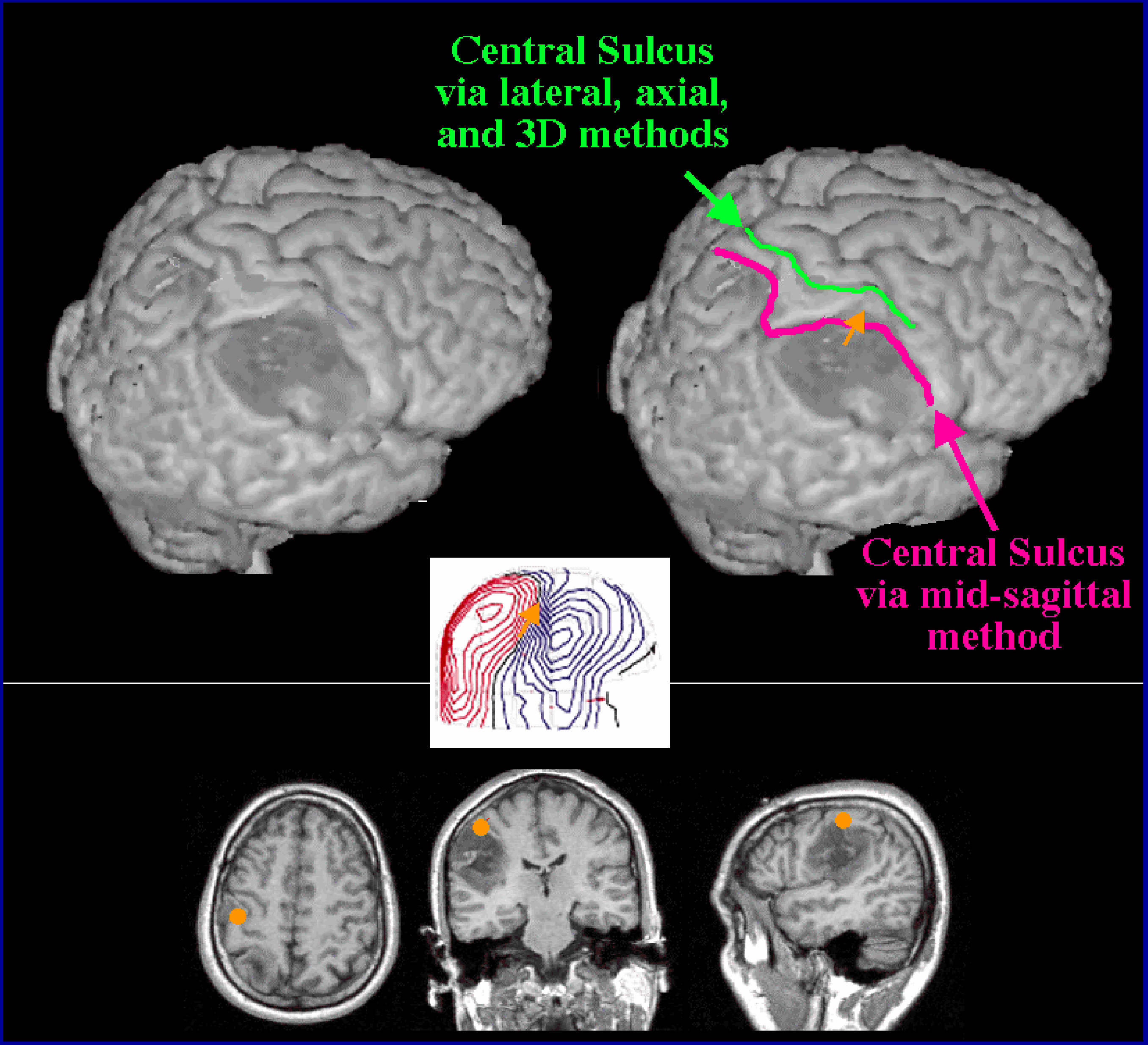
Results

- There were 2 patients where MEG data were uninterpretable.
- There were 12 patients where no MRI consensus was reached. MEG allowed for surgical decision in all 12.
- There were 16 additional patients where MEG changed patient care (5 did not have surgery because of MEG, 11 did have surgery with no post-surgical motor compromise for 10*)

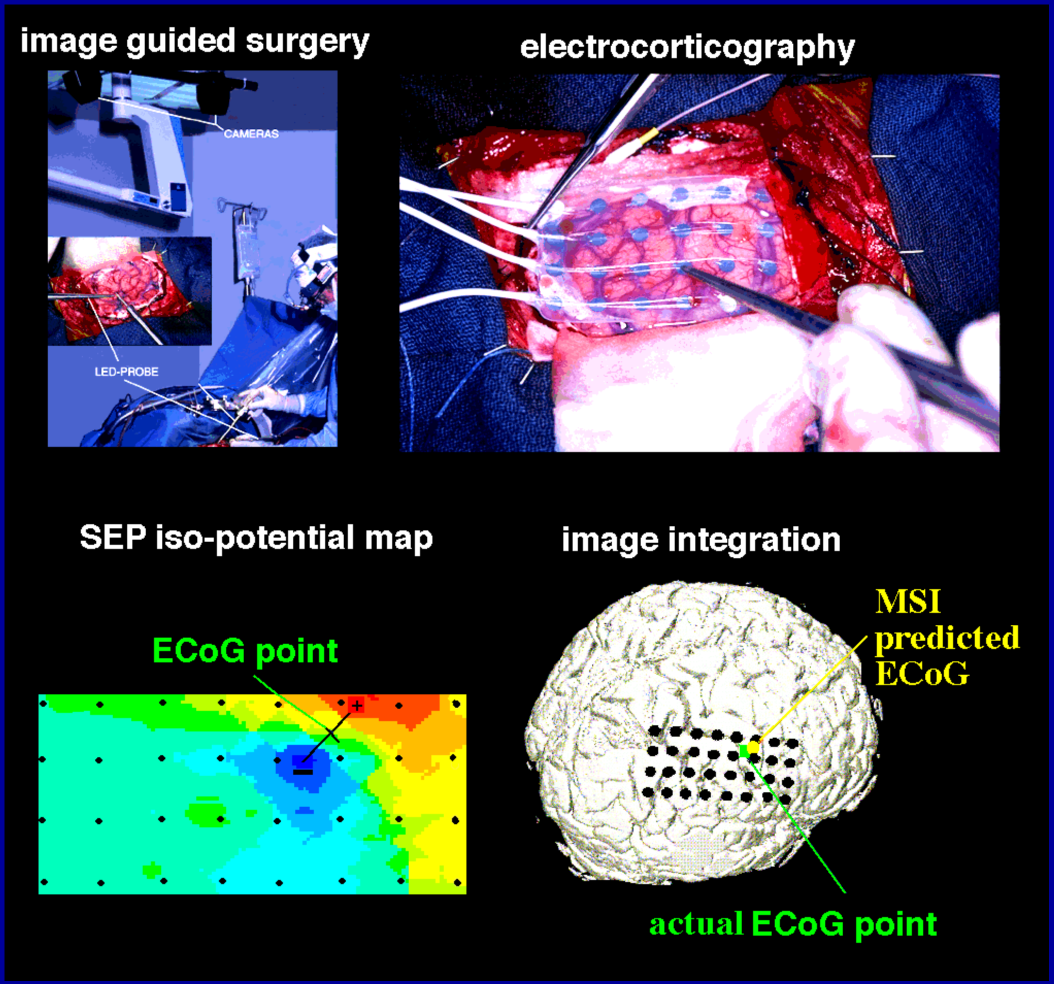
- * one patient, initially free of compromise had a small stroke on post-surgical day 2 which caused a subsequent partial paralysis.

Results

- 98 patients underwent surgery
  - intra-operative monitoring was performed in 78 cases. MEG inferences were correct in all cases (except the two where MEG made no prediction). MRI inferences were incorrect in 7 cases, and there were 11 cases MRI had made no prediction.


Central Sulcus
via lateral, axial,
and 3D methods
Central Sulcus
via mid-sagittal
method

Stereotaxic intraoperative procedures show that MEG/MSI based localizations of sensorimotor regions are accurate to within less than 6 mm

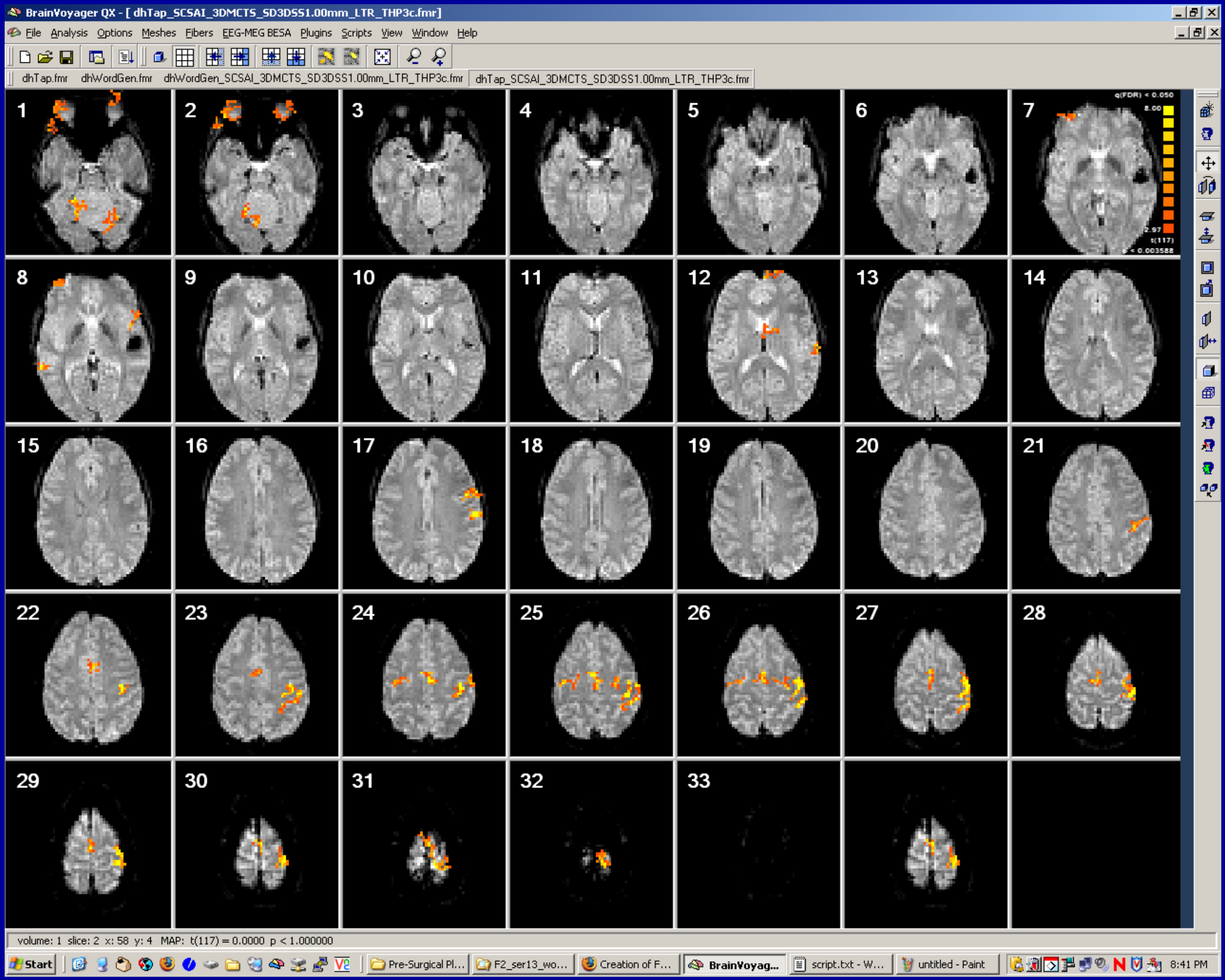


Lesion Type	MEG-ECoG corrected surface distance
Astrocytoma	07 mm
Astrocytoma	05 mm
Astrocytoma	02 mm
Astrocytoma	05 mm
Metastatic	07 mm
Metastatic	09 mm
Metastatic	05 mm
Metastatic	03 mm
average	05.4 mm
std	01.9 mm

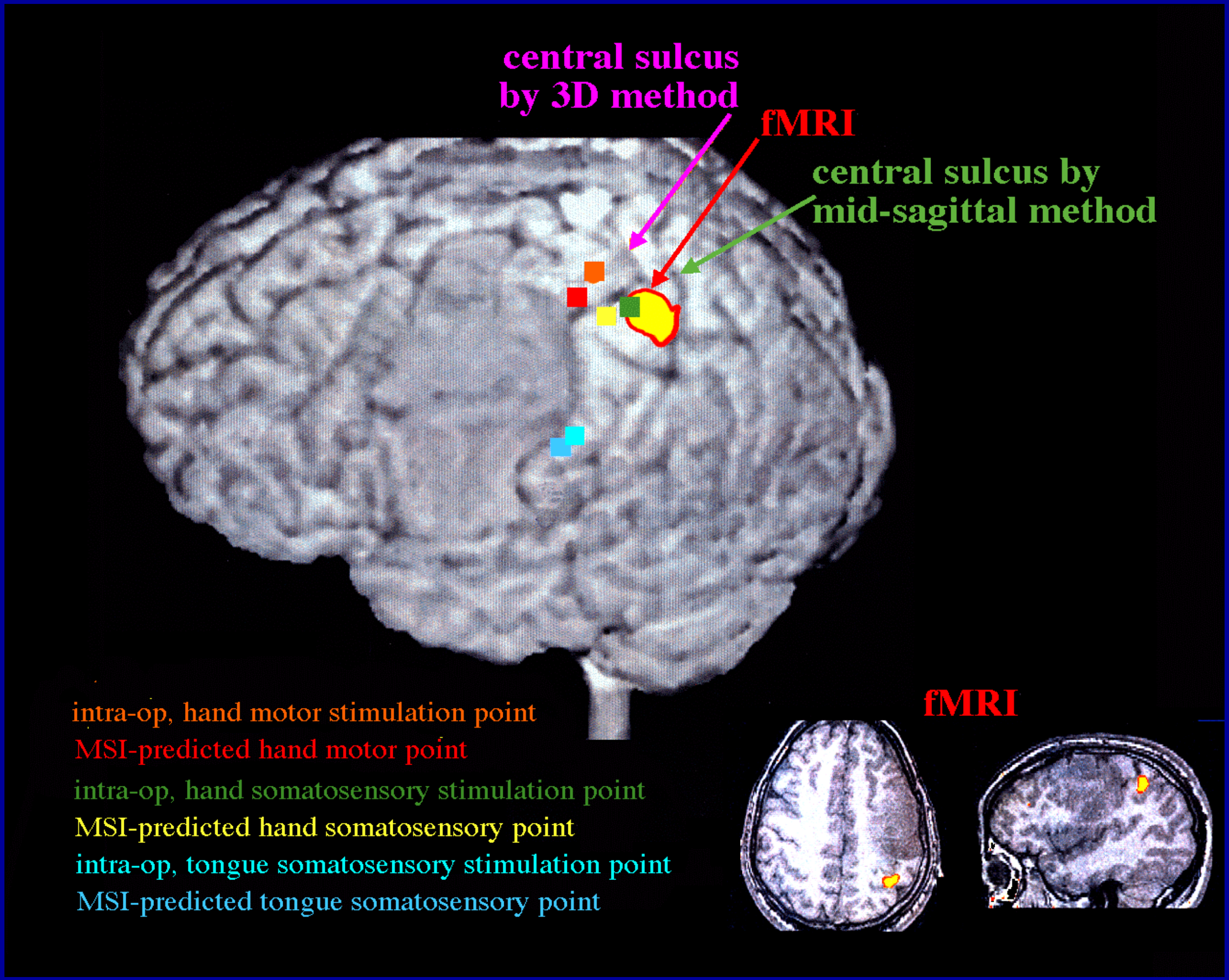
fMRI – good for somethings, but be careful

- Distinguishing motor from somatosensory activation can be difficult with fMRI
- fMRI fails in approximately 30% of patients with AVMs
- fMRI is difficult with children

fMRI gives multiple activations even for simple motor tasks



MEG temporal information can be critical in the identification of sensorimotor regions. In fMRI, it can be difficult to distinguish sensory from motor cortex, especially when pathology is present.



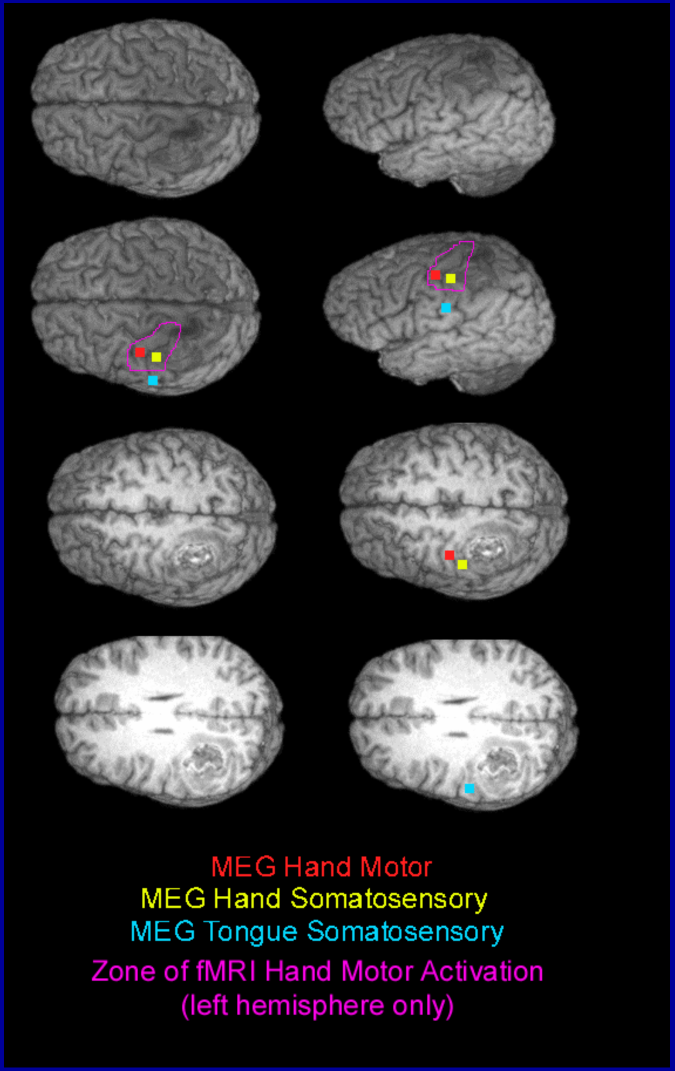
fMRI

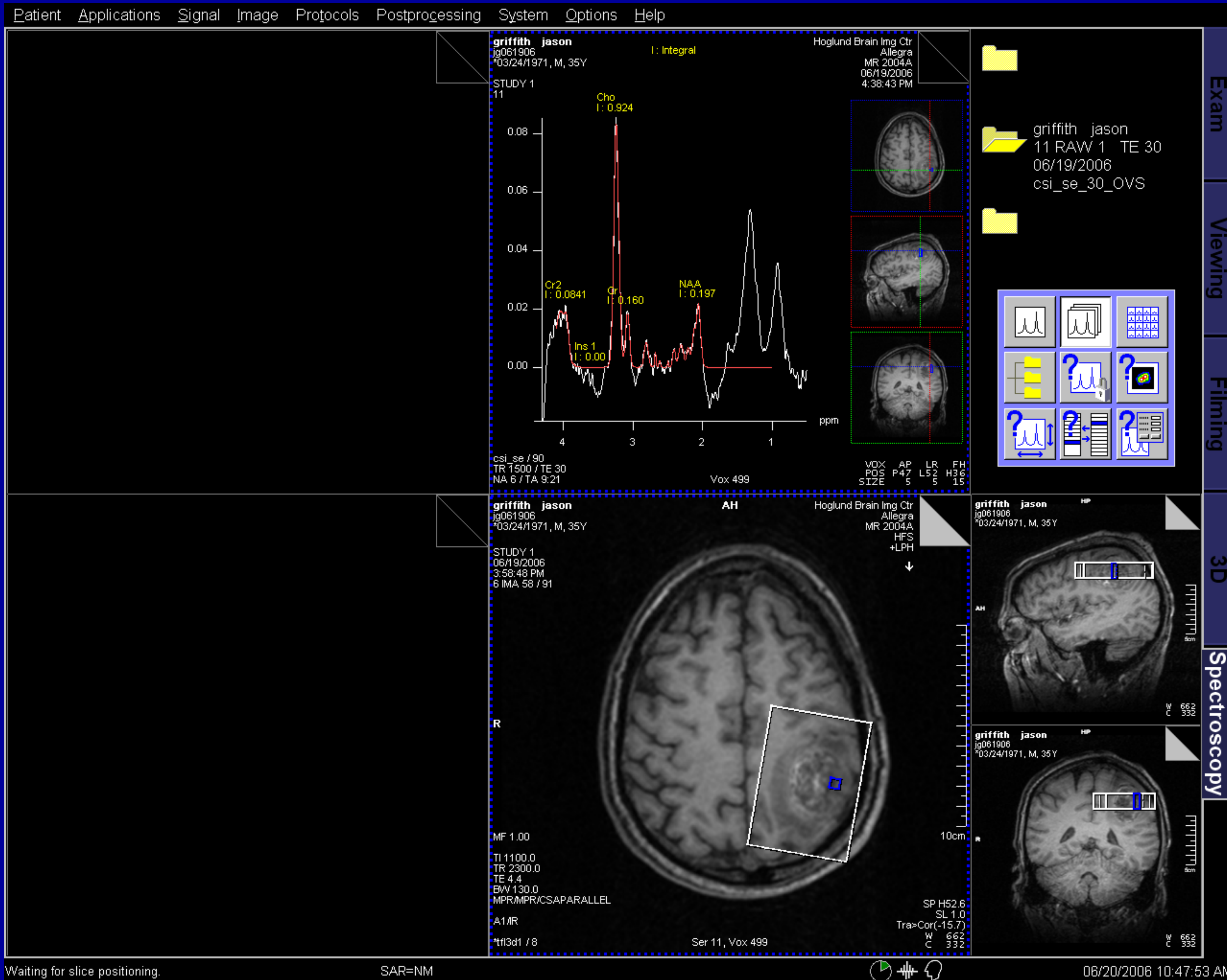
- 25 cases with frontal-parietal lesions
- fMRI failed in 2/5 AVM
- fMRI failed in 2 older patients with diabetes
- fMRI did not provide clear identification of CS in 6 cases because of multiple activities
- fMRI did not show any activation in 4 patients with lesions with large mass effect near the CS

Depending on the patient, it may be advantageous to perform both MEG and fMRI.
For example, fMRI is superior at localization of expressive language zones. Alexian Brothers also offers fMRI and MR spectroscopy procedures when needed, with MEG and MRI data all provided in a single integrated report.

	MEG	fMRI
somatosensory	+++	+ multiple activations
motor	++	+ multiple activations
Language laterality	+++	+++
Expressive Language	+	+++
Receptive Language	++	+
Reading Network	++	++

Spectroscopy can be another useful method, especially for defining tumor margins




Patient Applications Signal Image Protocols Postprocessing System Options Help
griffith jason
jg061906
*03/24/1971, M, 35Y
I : Integral
Hoglund Brain Img Ctr
Allegra
MR 2004A
06/19/2006
4:38:43 PM
STUDY 1
11
Cho
I: 0.924
Cr2
I: 0.0841
Cr
I: 0.160
NAA
I: 0.197
Ins 1
I: 0.00
0.08
0.06
0.04
0.02
0.00
4
3
2
1
ppm
csi_se / 90
TR 1500 / TE 30
NA 6 / TA 9:21
Vox 499
VOX AP LR FH
POS P47 L52 H36
SIZE 5 5 15
griffith jason
11 RAW 1 TE 30
06/19/2006
csi_se_30_OVS
Exam
Viewing
Filming
3D
Spectroscopy
griffith jason
jg061906
*03/24/1971, M, 35Y
AH
Hoglund Brain Img Ctr
Allegra
MR 2004A
HFS
+LPH
STUDY 1
06/19/2006
3:58:48 PM
6 IMA 58 / 91
R
MF 1.00
TI 1100.0
TR 2300.0
TE 4.4
BW 130.0
MPR/MPR/CSAPARALLEL
A1/IR
*tfl3d1 / 8
10cm
Ser 11, Vox 499
SP H52.6
SL 1.0
Tra>Cor(-15.7)
W 662
C 332
griffith jason
jg061906
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Waiting for slice positioning.
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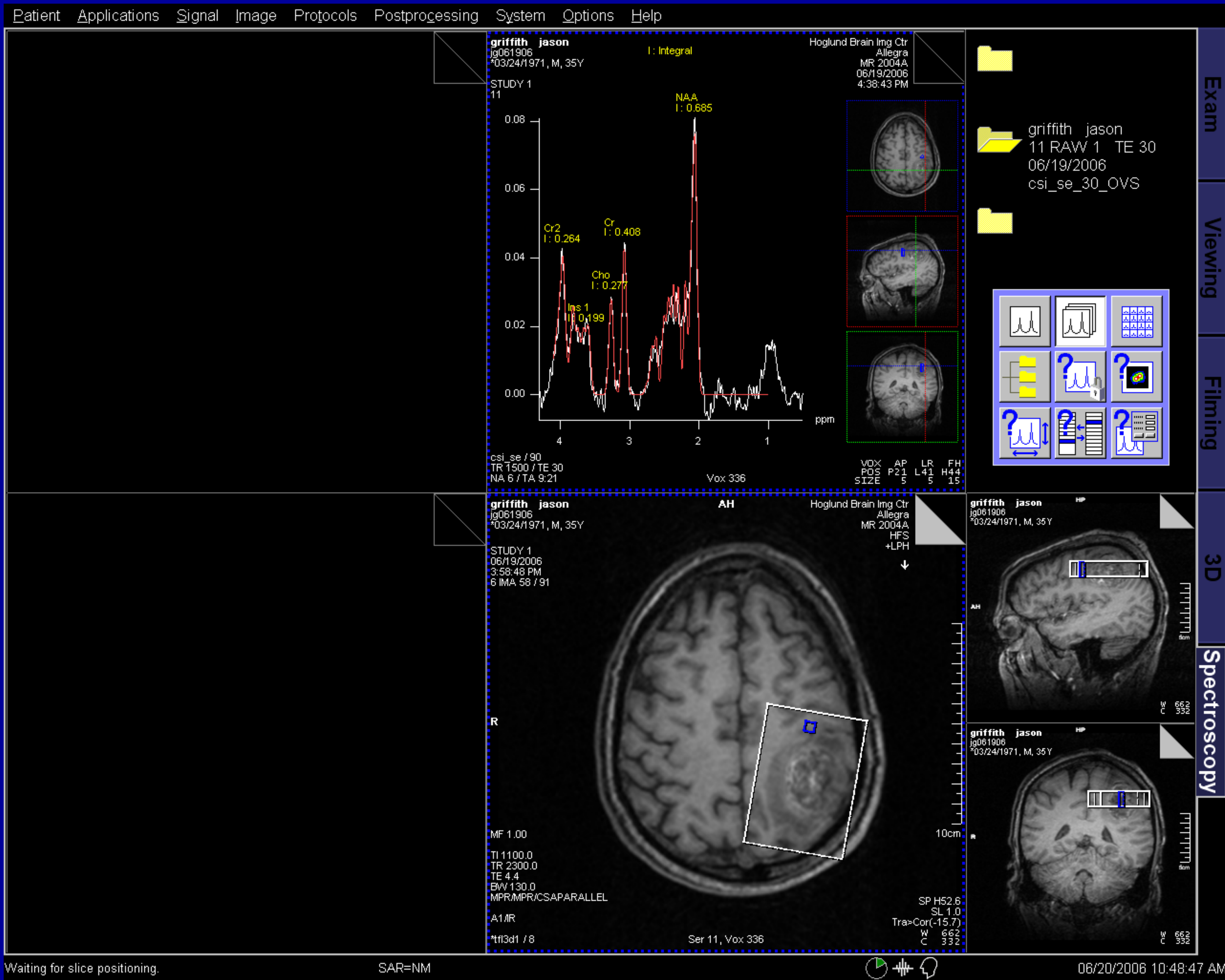

Patient Applications Signal Image Protocols Postprocessing System Options Help
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Hoglund Brain Img Ctr
Allegra
MR 2004A
06/19/2006
4:38:43 PM
STUDY 1
11
NAA
I: 0.685
Cr2
I: 0.264
Cr
I: 0.408
Cho
I: 0.277
Ins 1
I: 0.199
0.08
0.06
0.04
0.02
0.00
4 3 2 1
ppm
csi_se / 90
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NA 6 / TA 9:21
Vox 336
VOX AP LR FH
POS P21 L41 H44
SIZE 5 5 15
griffith jason
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06/19/2006
csi_se_30_OVS
Exam
Viewing
Filming
3D
Spectroscopy
griffith jason
jg061906
*03/24/1971, M, 35Y
AH
Hoglund Brain Img Ctr
Allegra
MR 2004A
HFS
+LPH
STUDY 1
06/19/2006
3:58:48 PM
6 IMA 58 / 91
R
MF 1.00
TI 1100.0
TR 2300.0
TE 4.4
BW 130.0
MPR/MPR/CSAPARALLEL
A1/IR
*tfl3d1 / 8
Ser 11, Vox 336
10cm
SP H52.6
SL 1.0
Tra>Cor(-15.7)
W 662
C 332
Waiting for slice positioning.
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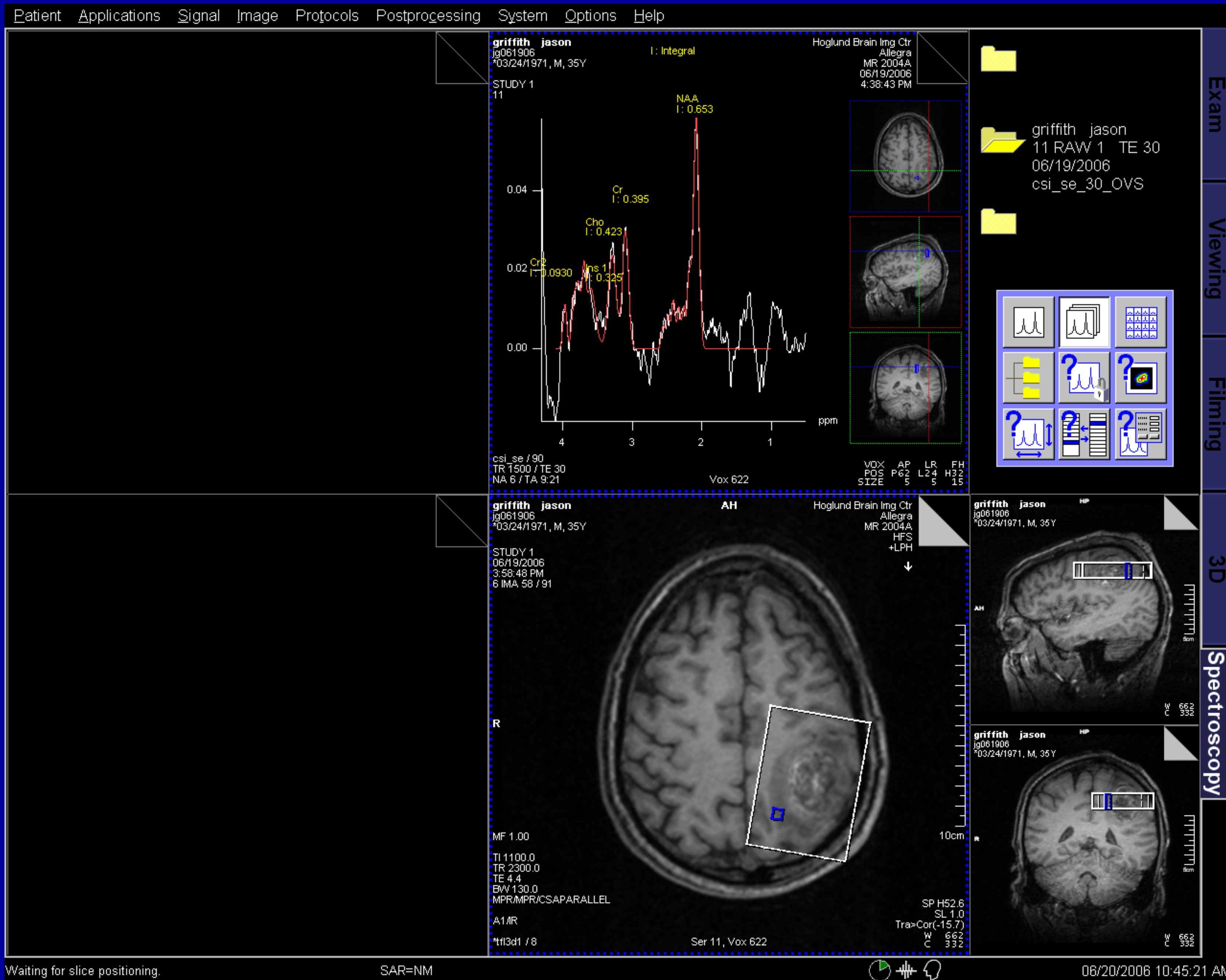
06/20/2006 10:48:47 AM


Patient Applications Signal Image Protocols Postprocessing System Options Help
griffith jason
jg061906
*03/24/1971, M, 35Y
STUDY 1
11
I : Integral
Hoglund Brain Img Ctr
Allegra
MR 2004A
06/19/2006
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NAA
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Cr
I : 0.395
Cho
I : 0.423
Cr2
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Ins 1
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3D
Spectroscopy
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Hoglund Brain Img Ctr
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MR 2004A
HFS
+LPH
STUDY 1
06/19/2006
3:58:48 PM
6 IMA 58 / 91
R
MF 1.00
TI 1100.0
TR 2300.0
TE 4.4
BW 130.0
MPR/MPR/CSAPARALLEL
A1/IR
*tfl3d1 / 8
Ser 11, Vox 622
10cm
SP H52.6
SL 1.0
Tra>Cor(-15.7)
W 662
C 332
griffith jason
jg061906
*03/24/1971, M, 35Y
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Waiting for slice positioning.
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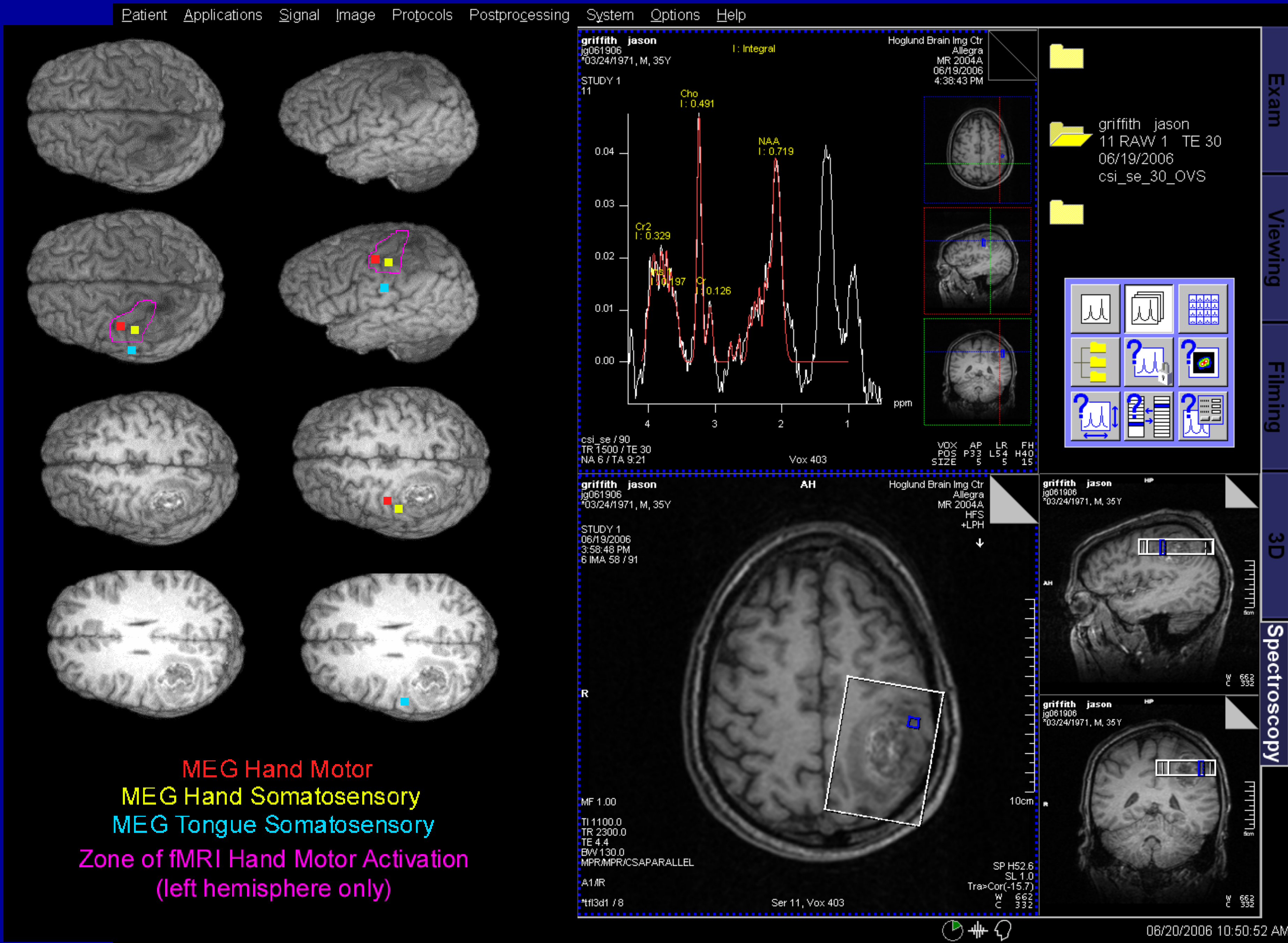
MEG Hand Motor
MEG Hand Somatosensory
MEG Tongue Somatosensory
Zone of fMRI Hand Motor Activation
(left hemisphere only)
Patient Applications Signal Image Protocols Postprocessing System Options Help
Exam
Viewing
Filming
3D
Spectroscopy
griffith jason
11 RAW 1 TE 30
06/19/2006
csi_se_30_OVS
Hoglund Brain Img Ctr
Allegra
MR 2004A
I: Integral
Cho I: 0.491
NAA I: 0.719
Cr2 I: 0.329
ppm
csi_se / 90
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NA 6 / TA 9:21
Vox 403
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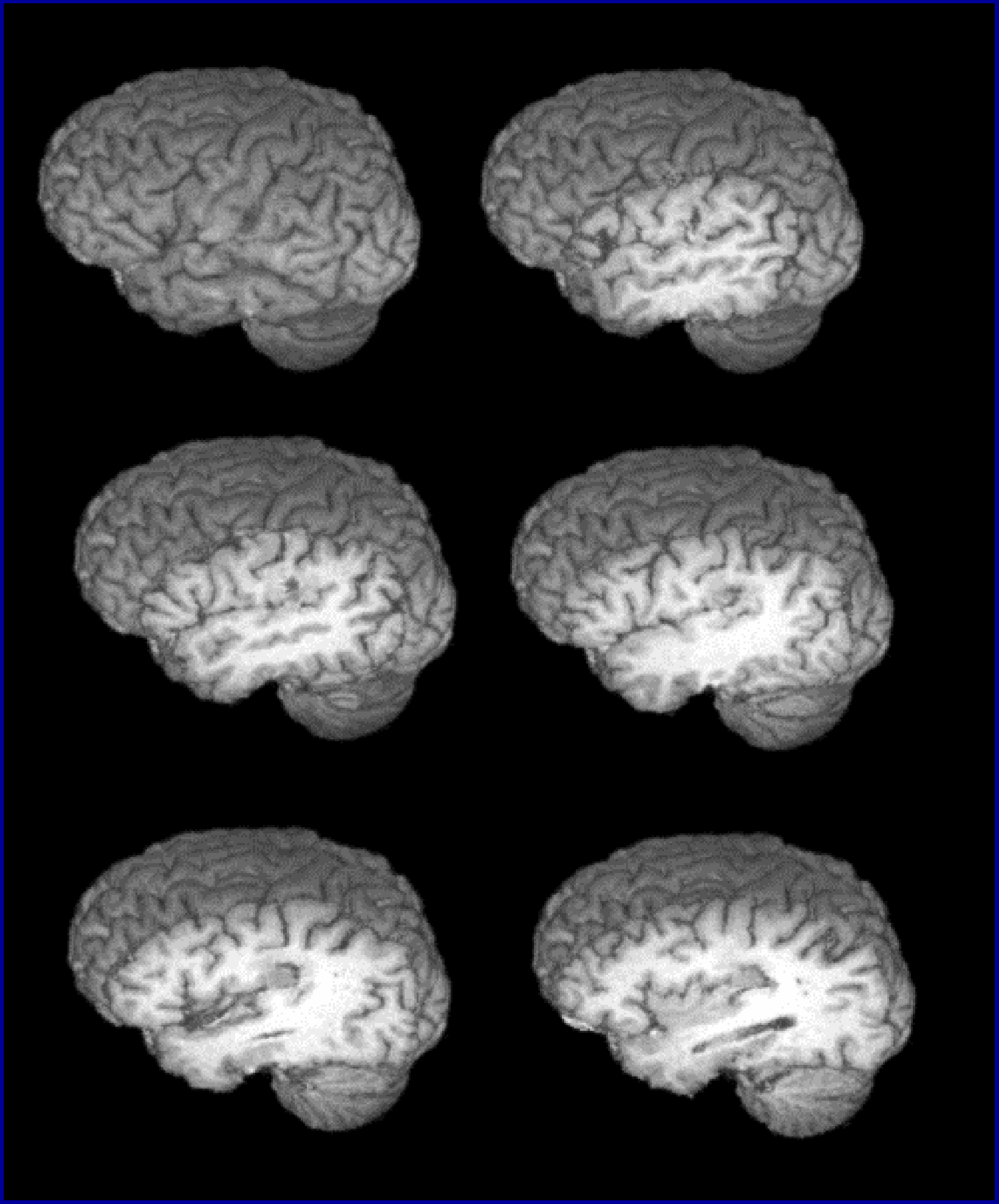
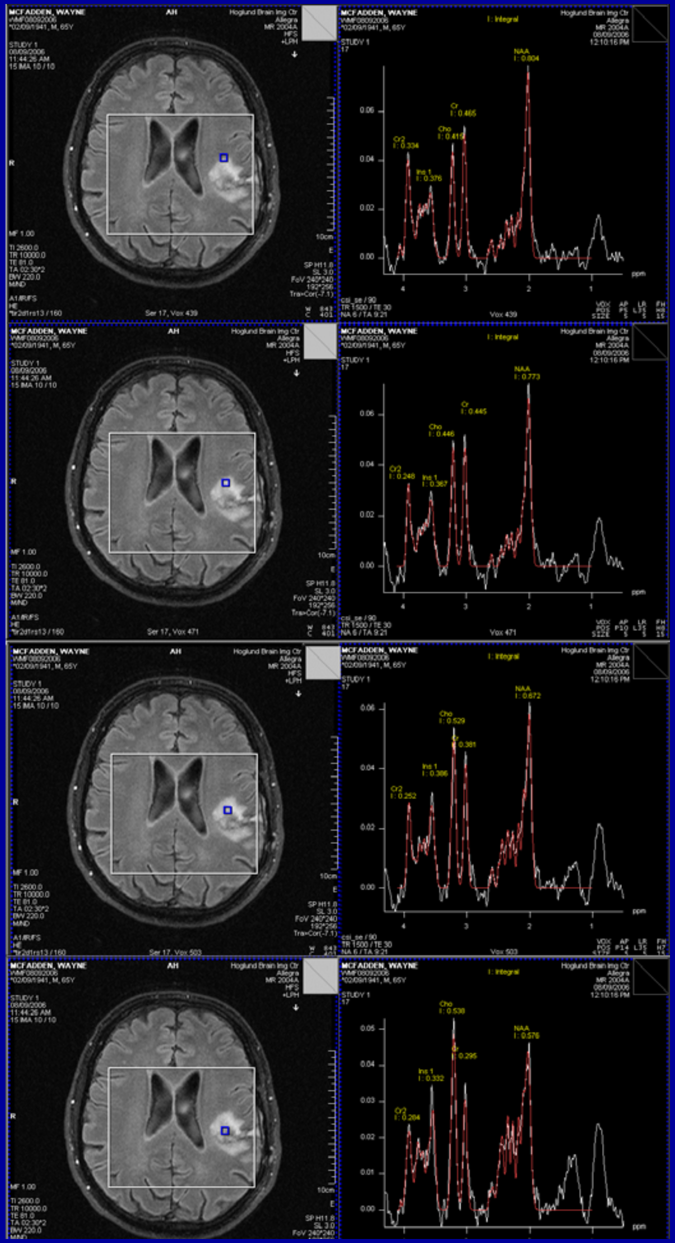
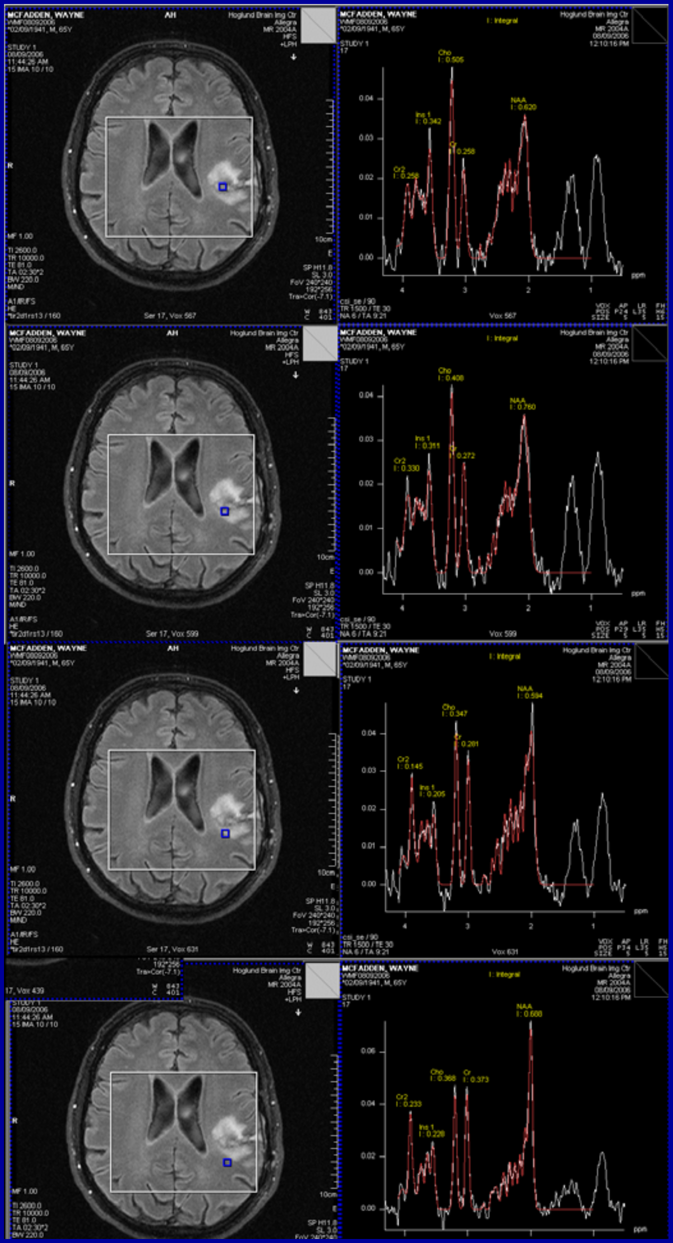
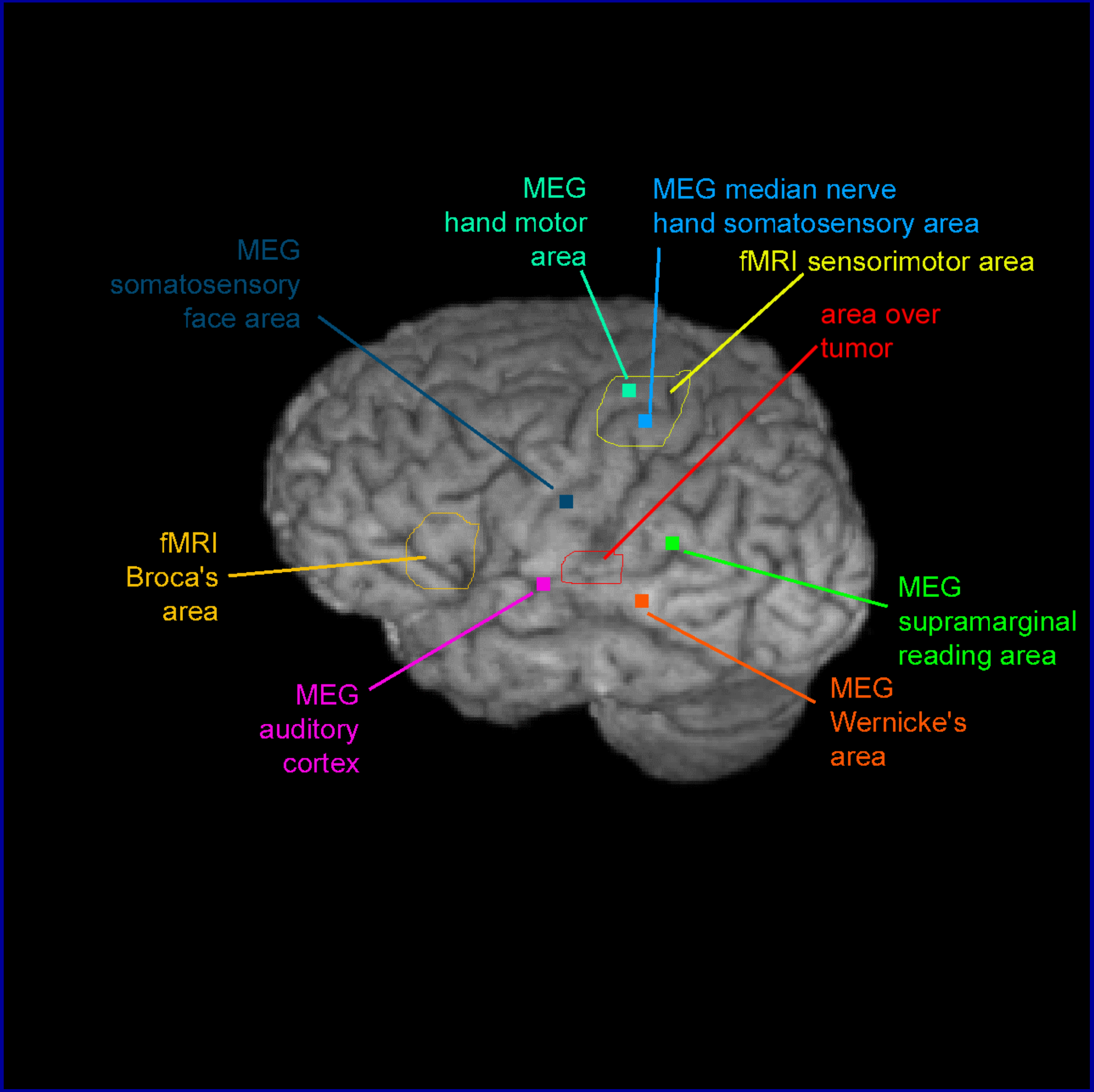
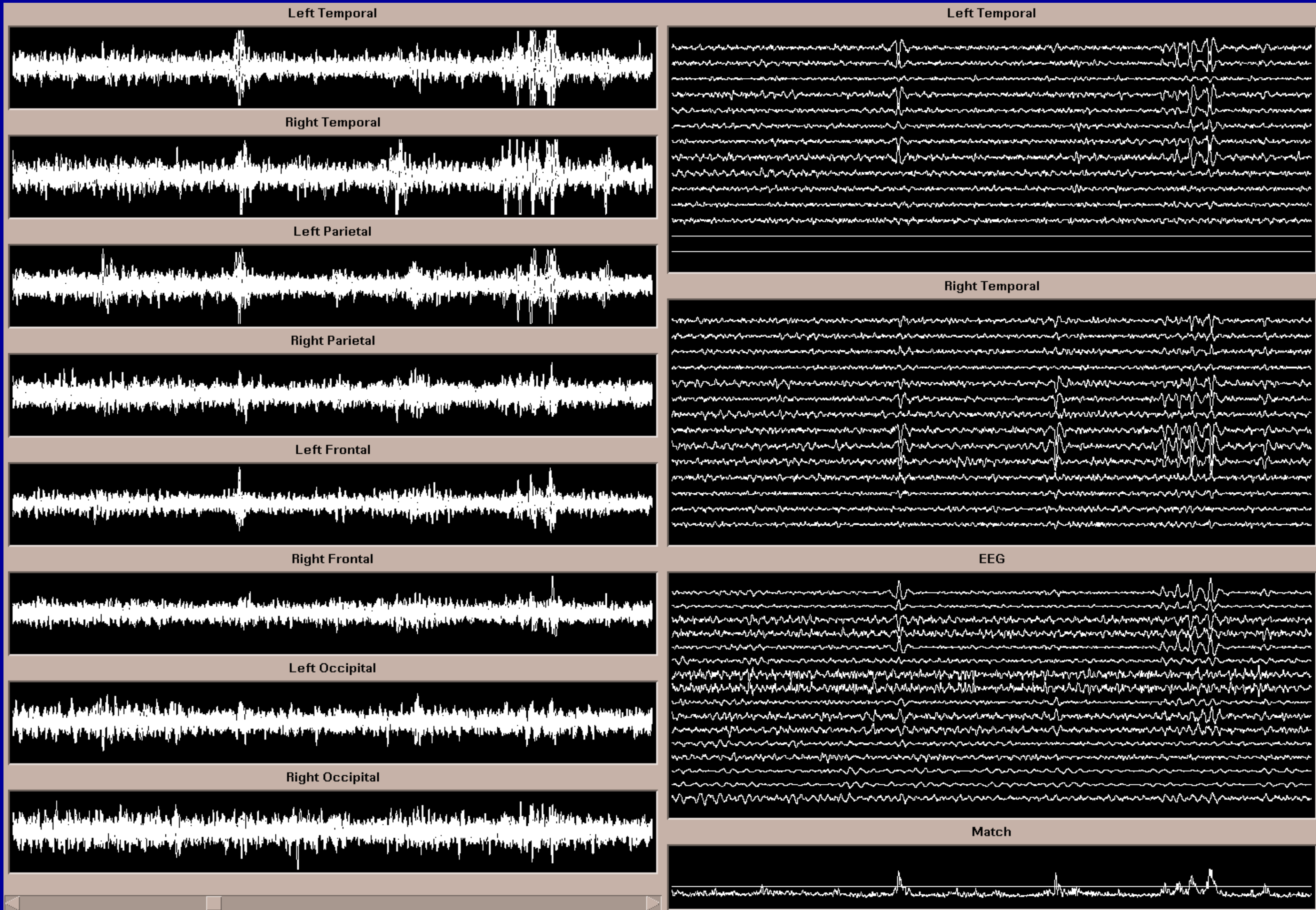


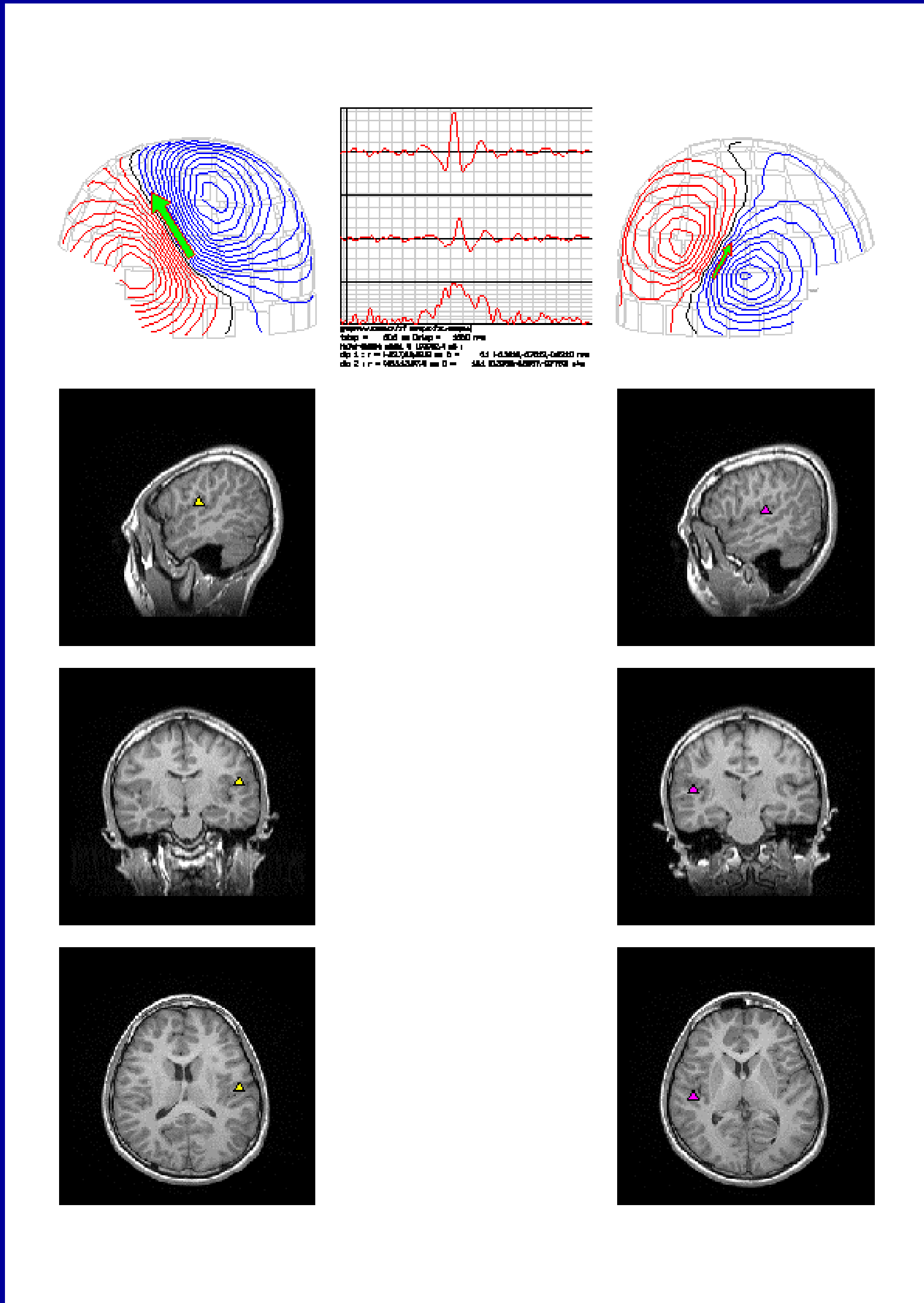


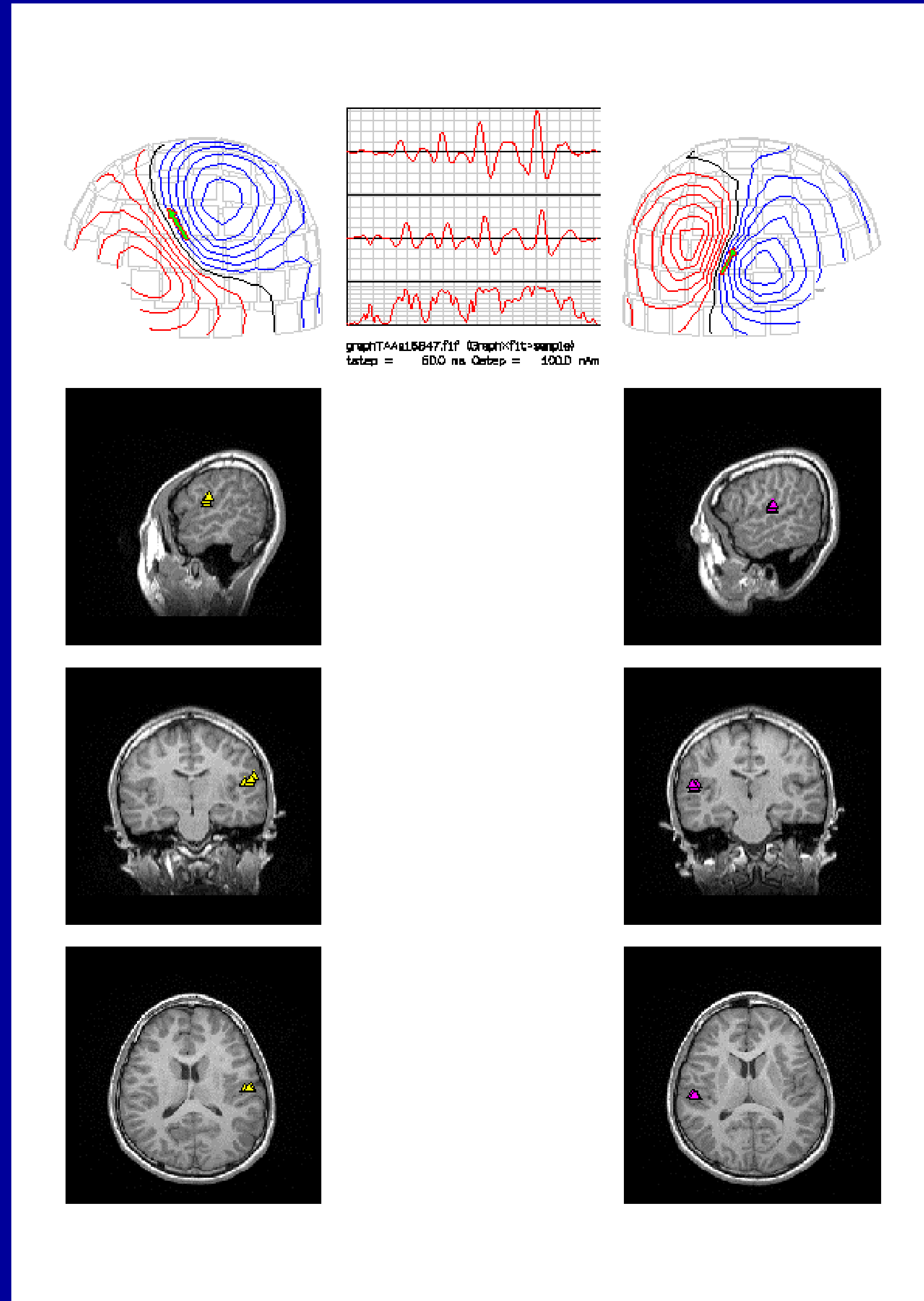




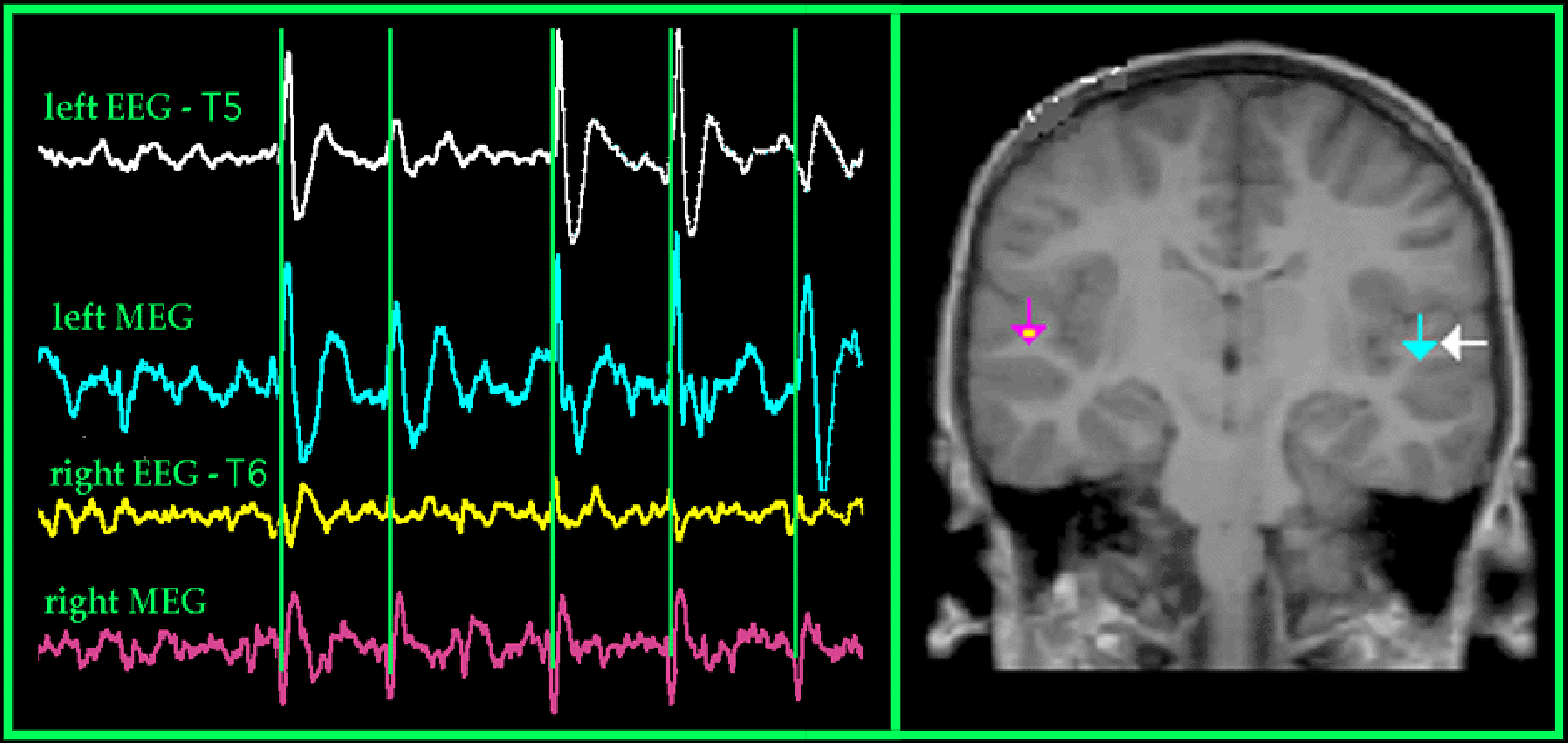
MEG
hand motor
area
MEG median nerve
hand somatosensory area
fMRI sensorimotor area
MEG
somatosensory
face area
area over
tumor
fMRI
Broca's
area
MEG
supramarginal
reading area
MEG
auditory
cortex
MEG
Wernicke's
area


Left Temporal
Right Temporal
Left Parietal
Right Parietal
Left Frontal
Right Frontal
Left Occipital
Right Occipital
Left Temporal
Right Temporal
EEG
Match

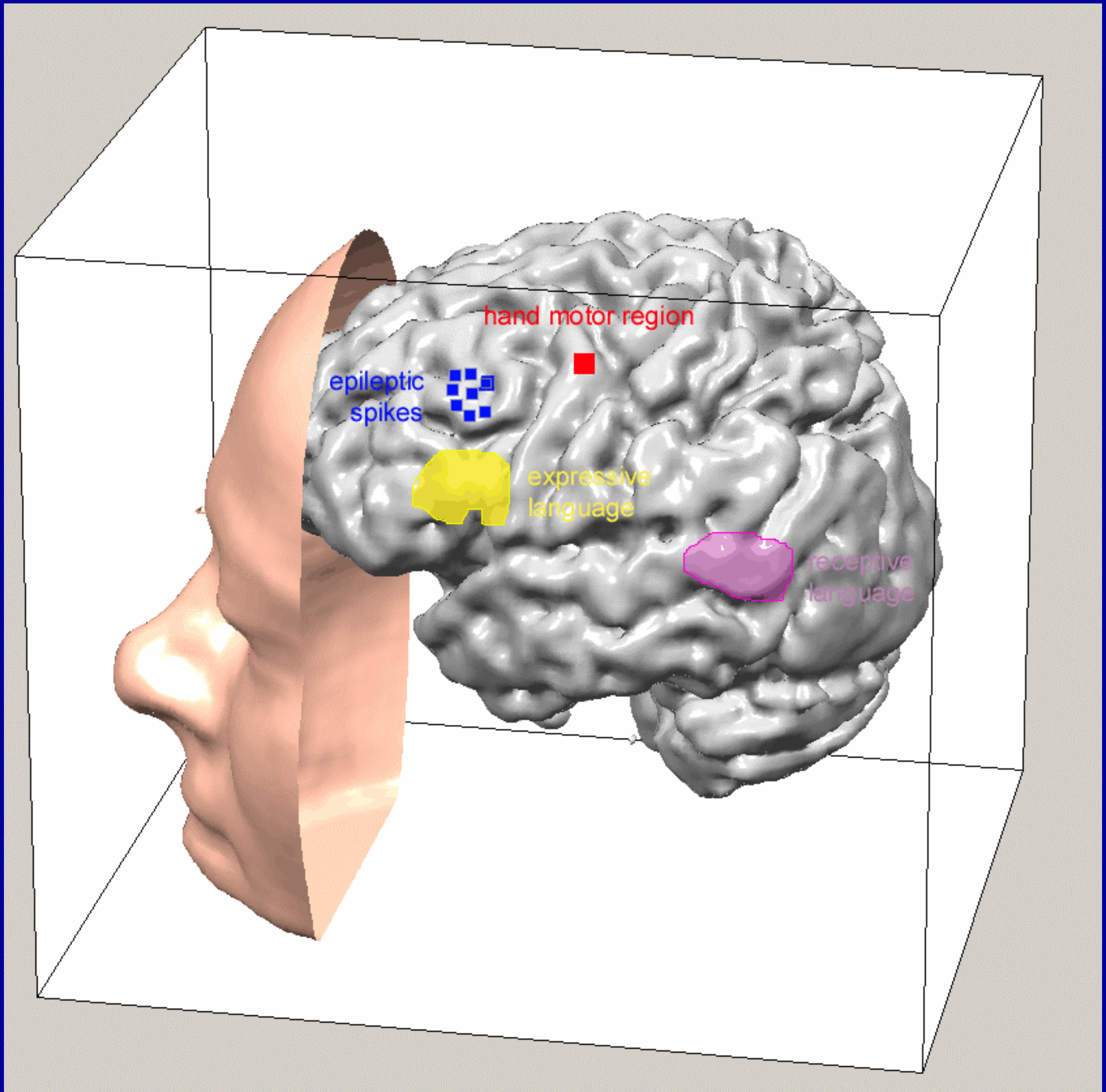



tstep = 60.0 ms Qstep = 100.0 nAm

Fp1
F3
F7
C3
T3
P3
T5
O1
Fp2
F4
F8
C4
T4
P4
T6
O2


left EEG - T5
left MEG
right EEG - T6
right MEG

25 year-old right handed male with left frontal epilepsy. MEG localized the spike zone and in combination with fMRI showed the region to be removed from both motor and language cortex. Resection led to a seizure free outcome



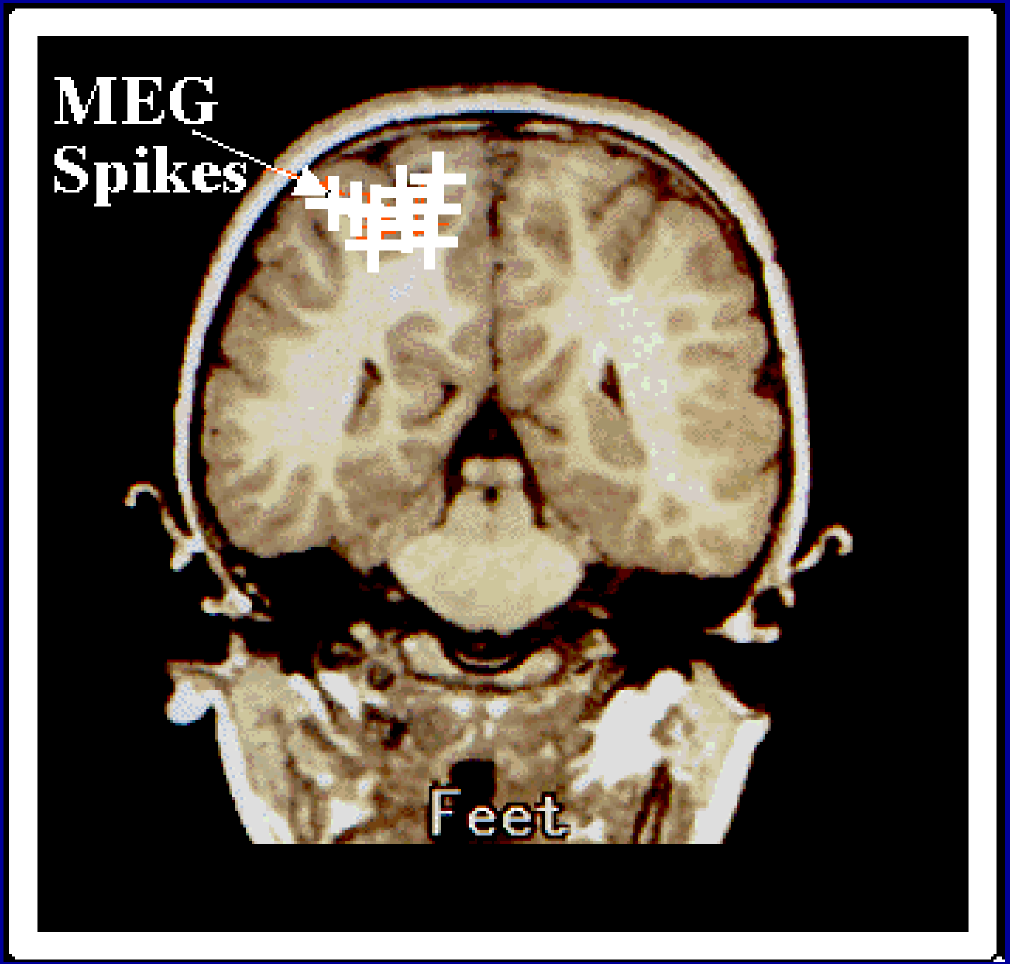
Predicting Outcome

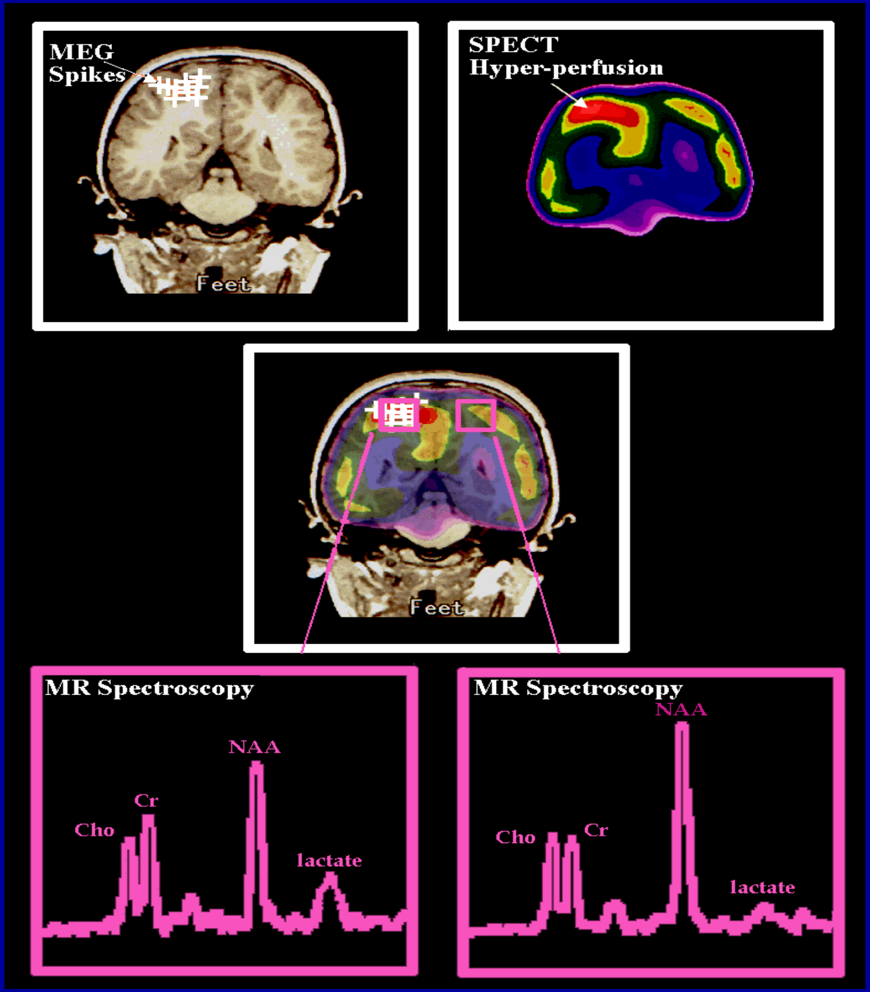
- 49 Non-lesional cases with corticography
- Surgery zone agreed with corticography in all cases.
  - 33/49 show good [type I/II] outcome ~67%
- Single MEG zone agreed with surgery in 35 cases
  - 30/35 show good outcome ~86%
- Single MEG zone disagreed with surgery in 7 cases
  - 2/7 showed good outcome ~29%
- Multiple MEG zone in 7 cases
  - 1/7 showed good outcome ~14%

Predicting Outcome

- 8 Non-lesional cases without corticography
  - Good outcome in all 8 with agreement between ictal EEG, interictal MEG, and one other method [SPECT, PET, or MRS]

Case Example: Extra-temporal non-lesional epilepsy. Integration with other methods may be of utility.





Conclusions

Multimodal Functional Brain Imaging is useful for guiding surgical interventions in patients with tumors, vascular malformations, and epilepsy.

MRS is the method of choice for defining tumor margins

MEG and fMRI contribute to mapping of eloquent cortex

MEG is a useful adjunct to video EEG and intracranial recordings in patients with epilepsy.

Clinical FMRI: Language Mapping

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Dept Psychiatry and Biobehavioral Sciences
UCLA School of Medicine
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Introduction to the problem:

why language mapping with fMRI is shockingly different from language research or standard radiology

- For surgical planning: relate *activation* to *disruption*
  - Not exploratory: can't interpret blobs post-hoc
  - Interpretations based on knowledge of the language system and effects of damage- all within subject
  - Have to know the functional systems extremely well
- Make recommendations, predict outcomes
  - Integrate fMRI findings with surgical plan; outcome data, validation data
  - If we are wrong, patients become aphasic
  - We can get sued

Team members

- Language expert: someone who knows both language activation patterns and lesion deficit relations (usually a neuropsychologist; behavioral neurologist, linguist, speech pathologist
- fMRI expert (image quality, analysis)
- MRI interpreter (usually a neuroradiologist; surgeon, neurologist)
- Psychometrist (neuropsychologist, clinical psychologist, speech pathologist)
- Referring physician (neurosurgeon; neurologist)

Clinical fMRI: Within-subject

- Clinical fMRI has CPT code for pre-surgical planning: Motor, sensory, language
  - **70554 Functional MRI NOT REQUIRING physician or psychologist administration**
  - **70555 Functional MRI REQUIRING physician or psychologist administration**
- Question: Where are the critical functional areas (eloquent cortex)
  - Intra-hemispheric (know which hemisphere you are going to operate on)
  - Laterality

Within-subject clinical design

- Statistical concern is false negatives
  - Far less tolerant of noise from any source
  - Baseline conditions are a major concern
  - Isolation of variables in “cognitive subtraction” more risky
- Unique problems with lesion-induced artifact
- Performance variables are critical
  - Many patients have deficits
- Unique and unexpected patient needs
  - primary language is Swahili; pt. is a musician

Task design for within-subject experiments

- Blocked vs single trial?
  - blocked
- How many conditions?
  - As few as possible (2)
- What tasks?
  - At least 3
  - Tailor tasks to lesion; know your task
- How to isolate “eloquent” areas
  - Do you tailor control tasks in the “cognitive subtraction” tradition?

Additive factors assumptions

- You have correctly identified and isolated the variable(s) intended
- Linearity/additivity
- In additional hierarchical levels, “controlled” processes do not change
- All of these assumptions are false

- Potential solutions:
  - Low level baseline (fixation)
  - Parametric designs (have to carefully evaluate performance within subject)

Referral Questions

- Laterality of language
  - Left handers; children; epilepsy, AVM (childhood onset lesions)
  - Is an invasive procedure necessary (Wada, corticography)?
- Intra-hemispheric organization of language
  - Large majority of referrals
  - Brain tumors, LH AVMs, etc.
  - Is the lesion resectable? Is corticography necessary? What is the best route to the lesion? What risks does the patient face?

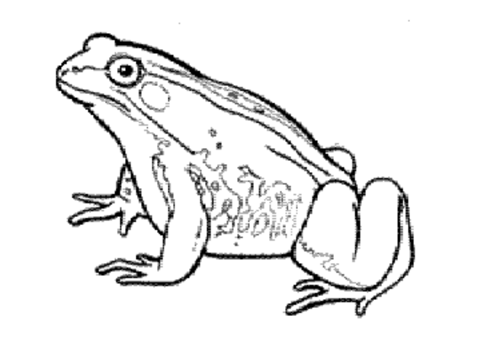
Before you start

- Make sure you know the referring physicians goals and the patient's priorities
- Establish patient ability/deficit level -- use tasks at the ability level appropriate for the patient (psychometrist; screening tool)
- Choose tasks of relevance to the region you care about
  - Frontal lesion: expressive speech tasks
  - Temporal lesion: comprehension tasks that differentiate A1 from WA
- Modify tasks as needed (other languages)

Basic Mapping Approach

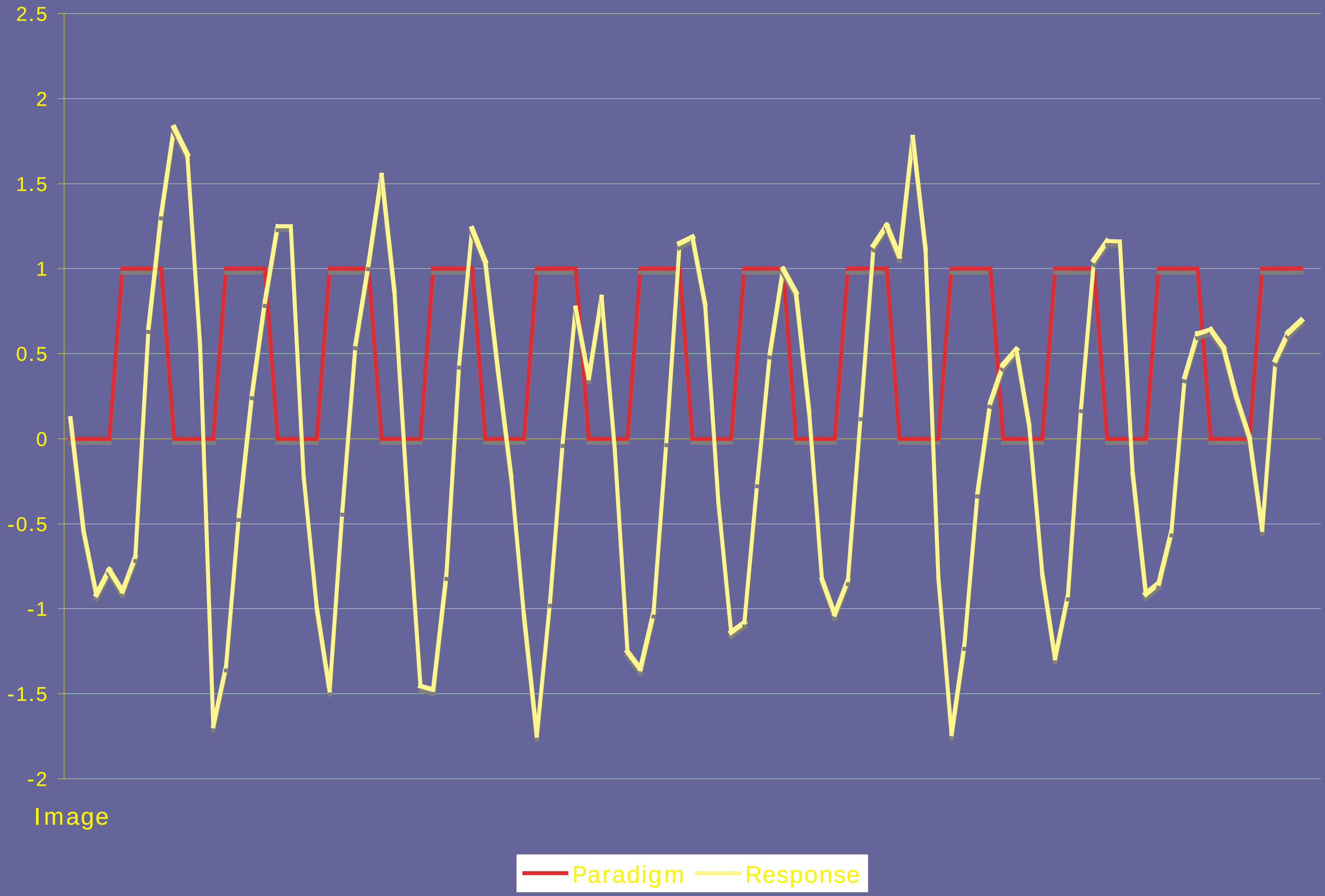
- Use multiple tasks with low level baseline
  - Don’t want to “subtract” a critical function activated passively
- Look for areas of consistent overlap
- Look for task-specific effects
- Focus on region of interest--function of interest
- Ensure quality control at each step

Multiple tasks, multiple modalities



- Object/action Naming
- Auditory Naming
  - Smell with this "nose"
- Reading/naming
  - "tall pink bird"
- Find conjunction
  - Comprehension, expression
- Other tasks: generation, sentence processing, region specific tasks; patient-specific tasks (reading music)

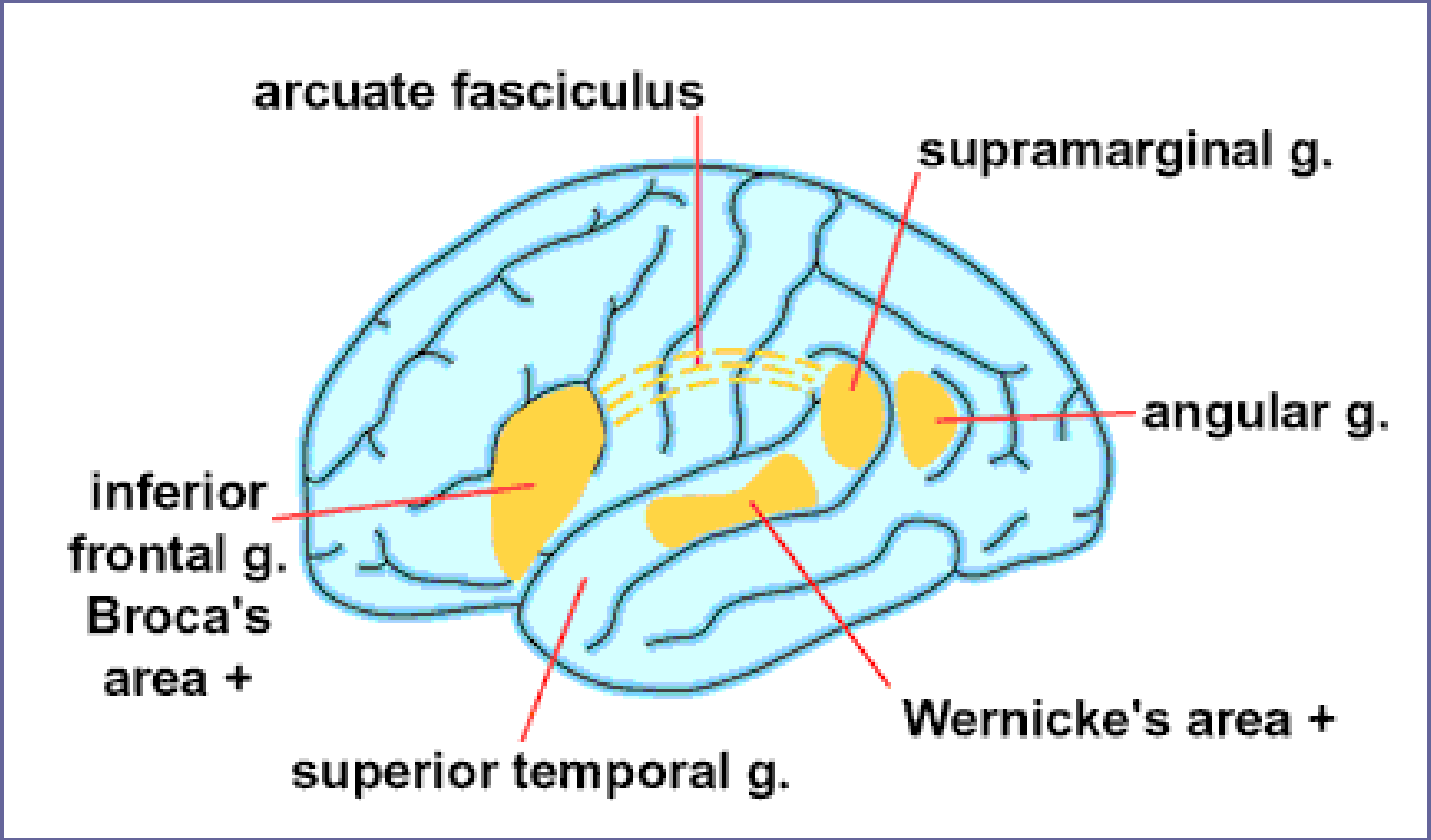
Short blocked paradigm



Conjunction analysis

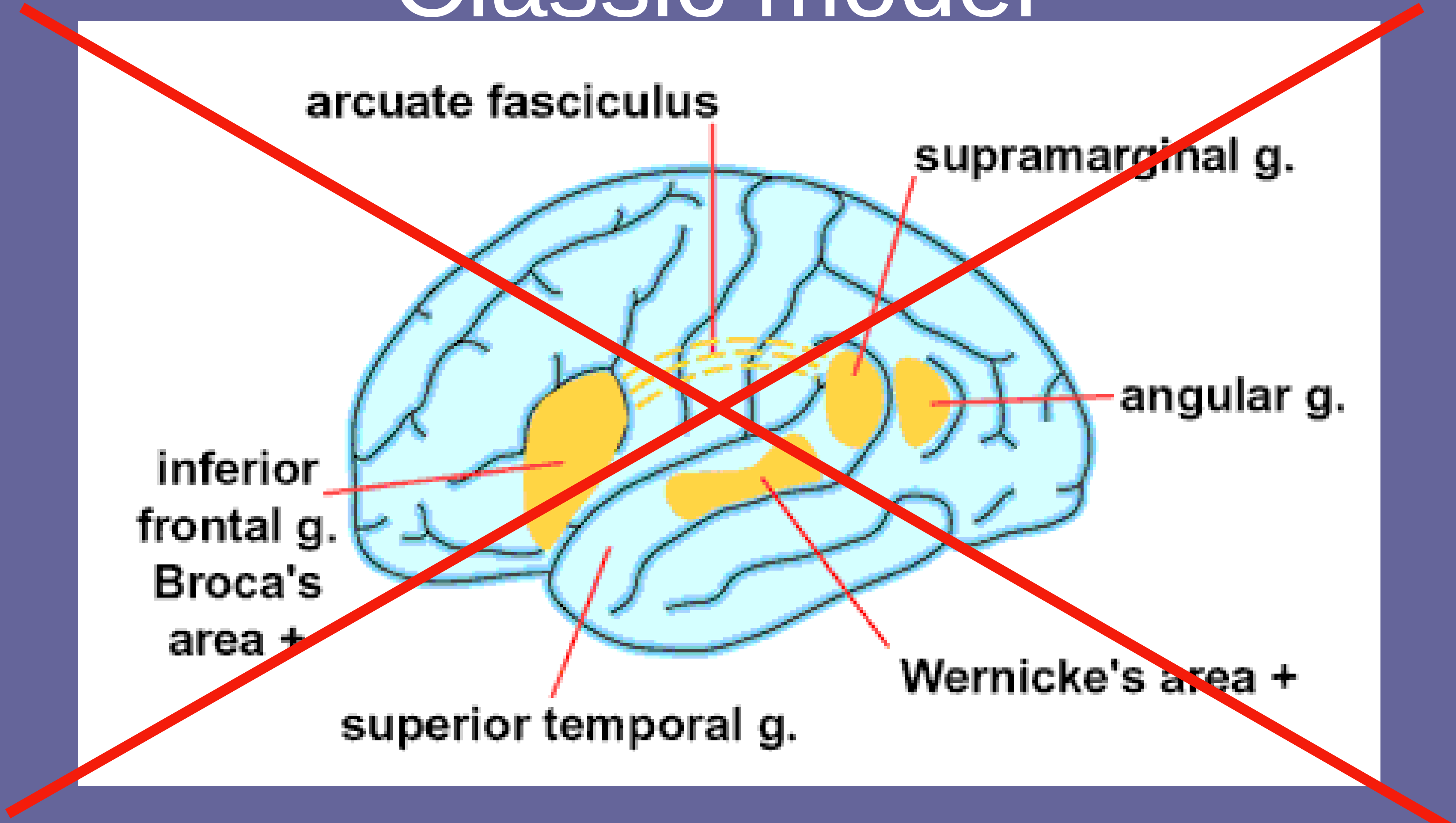
- Logical AND
- Areas consistent across tasks, different sensory input
- Sensitive to low level activation
- Insensitive to random noise (noise or chance probability of activation = **product** of chance activation in each task) ie, $p<.05 \times .05 \times .05 < .000125$

Language Organization
Classic model

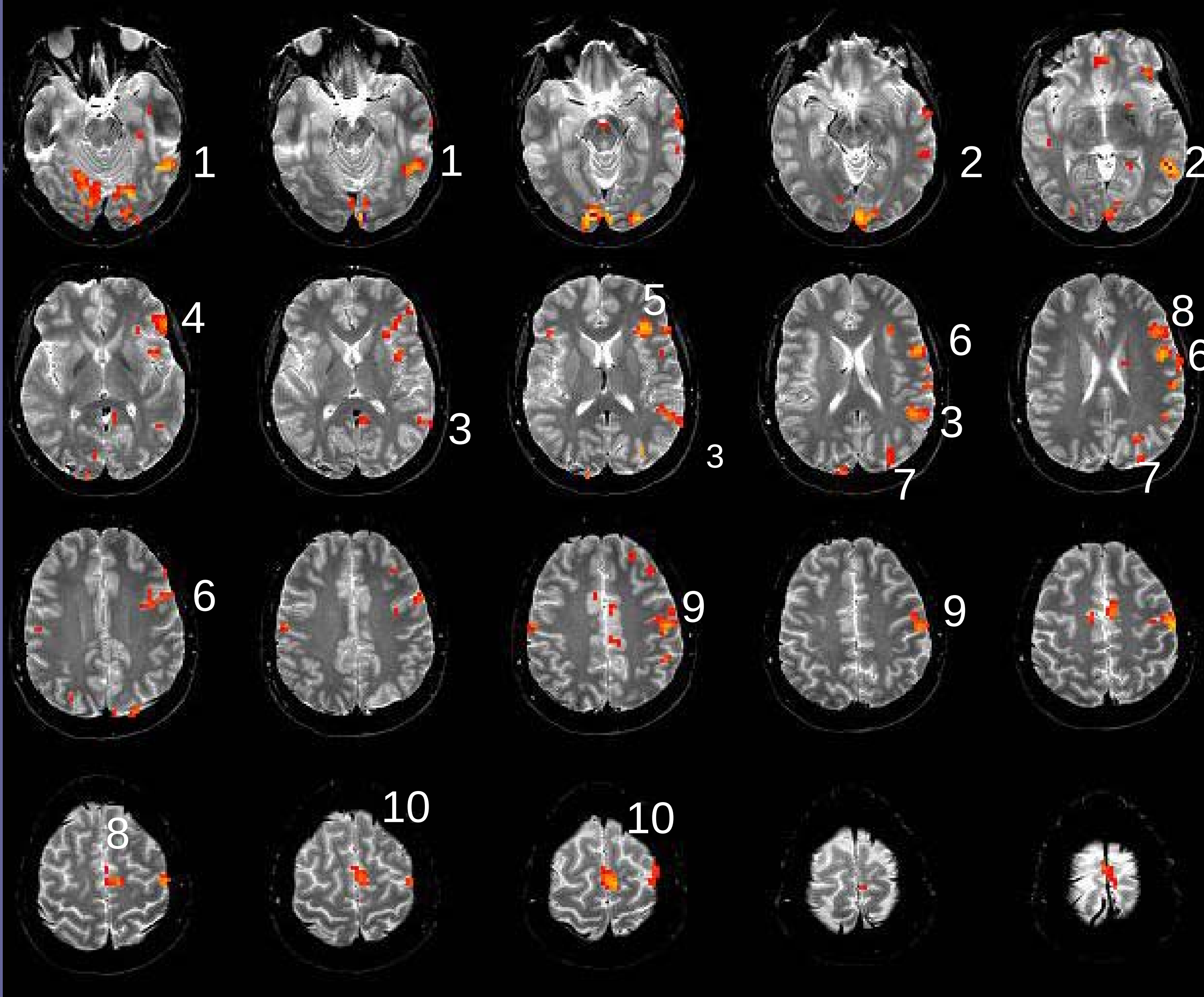


Sensory perception--comprehension (WA)--Broca’s (formulation, motor plan)--motor cortex (final common pathway)

Language Organization
Classic model



Sensory perception--comprehension (WA)--Broca's (formulation, motor plan)--motor cortex (final common pathway)


1
1
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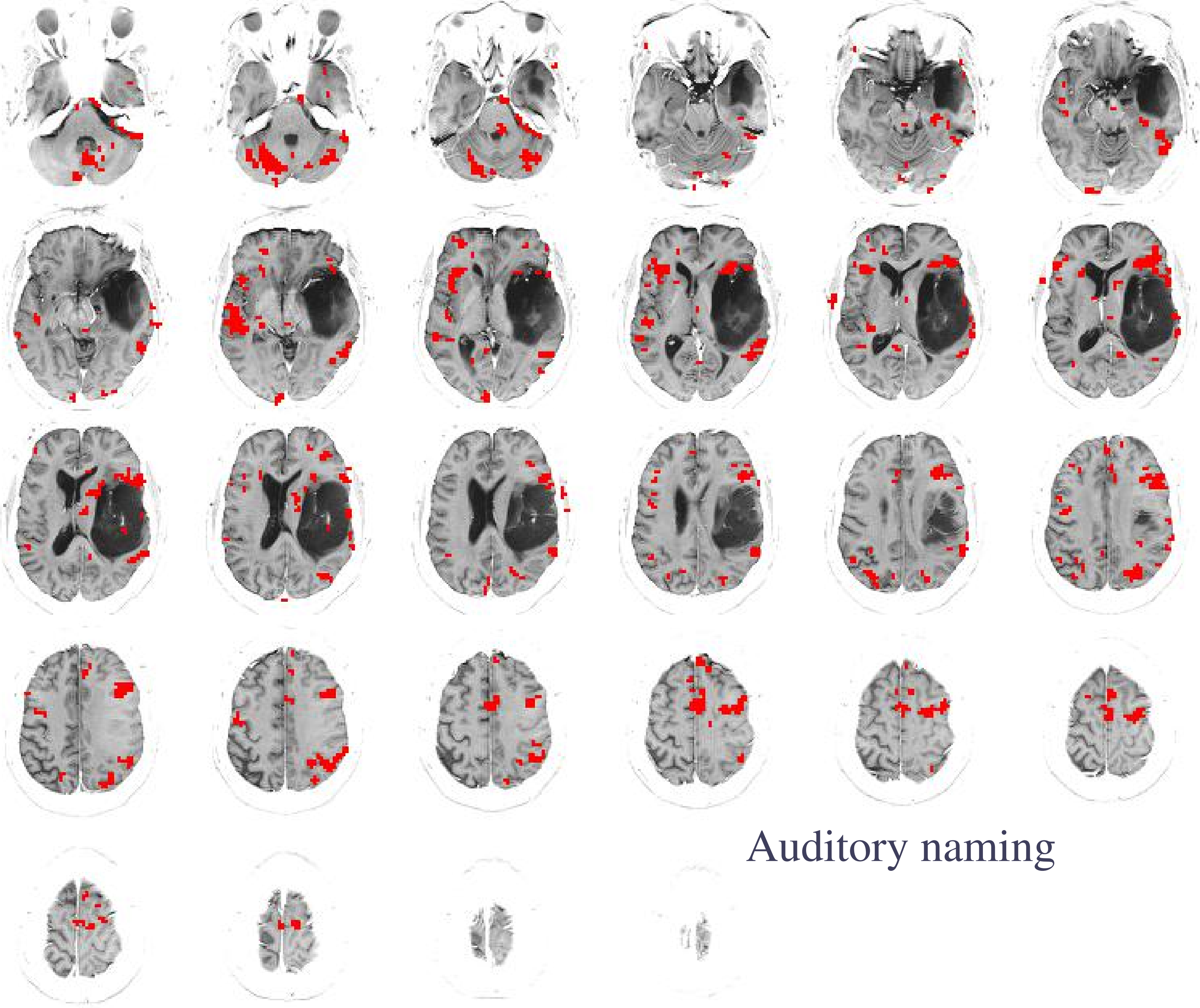
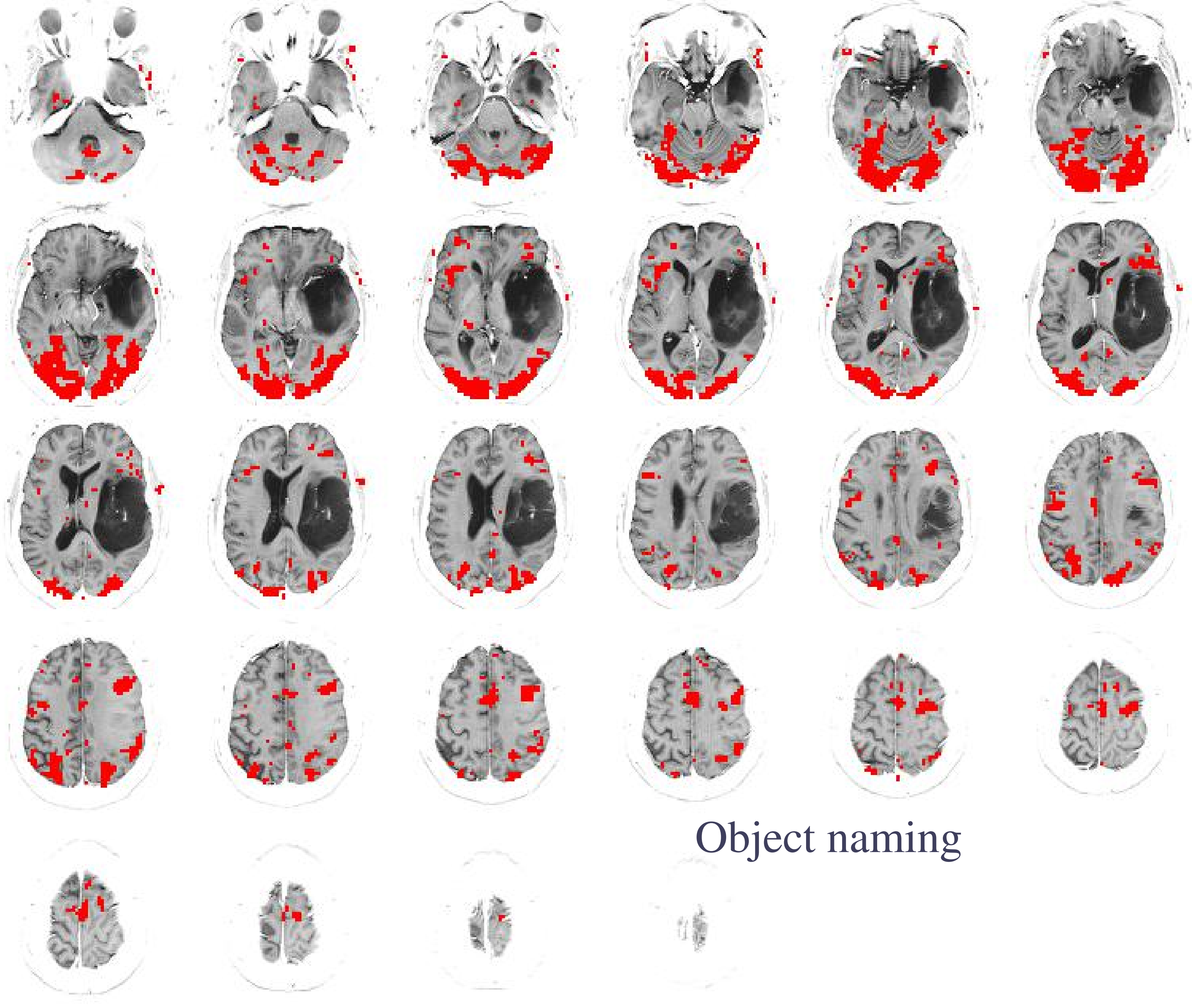
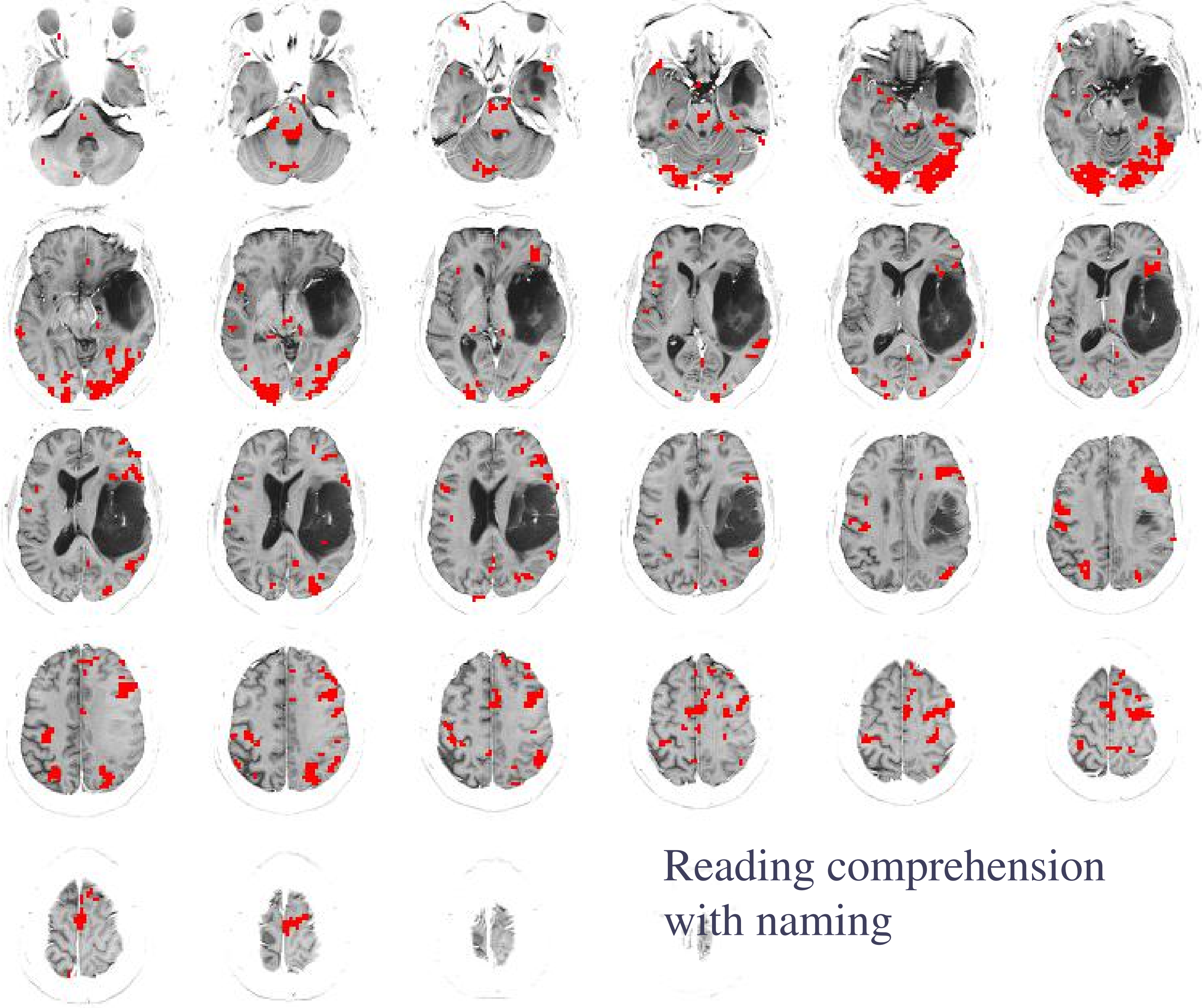
3
7
8
6
7
6
9
9
8
10
10



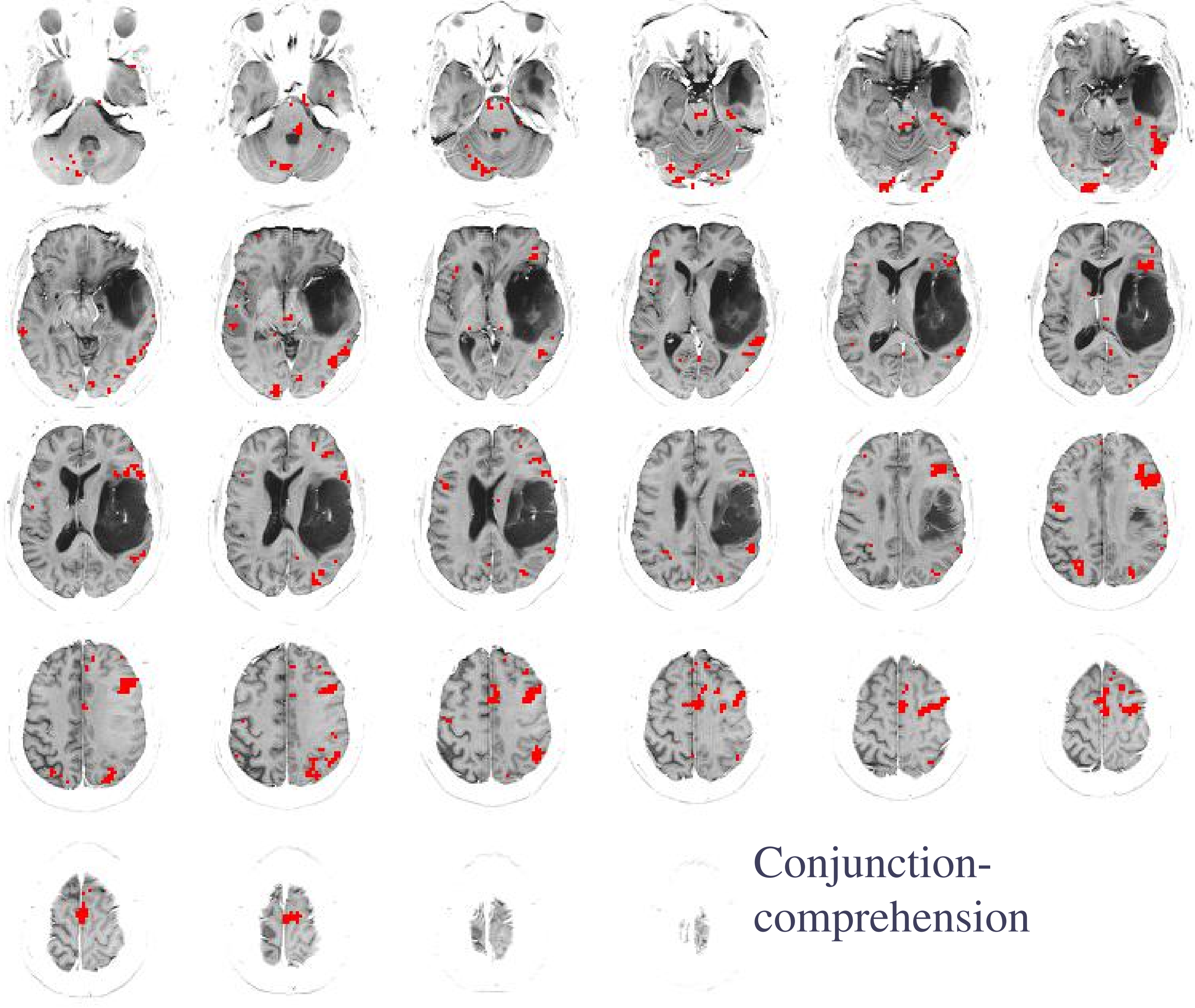
Auditory naming



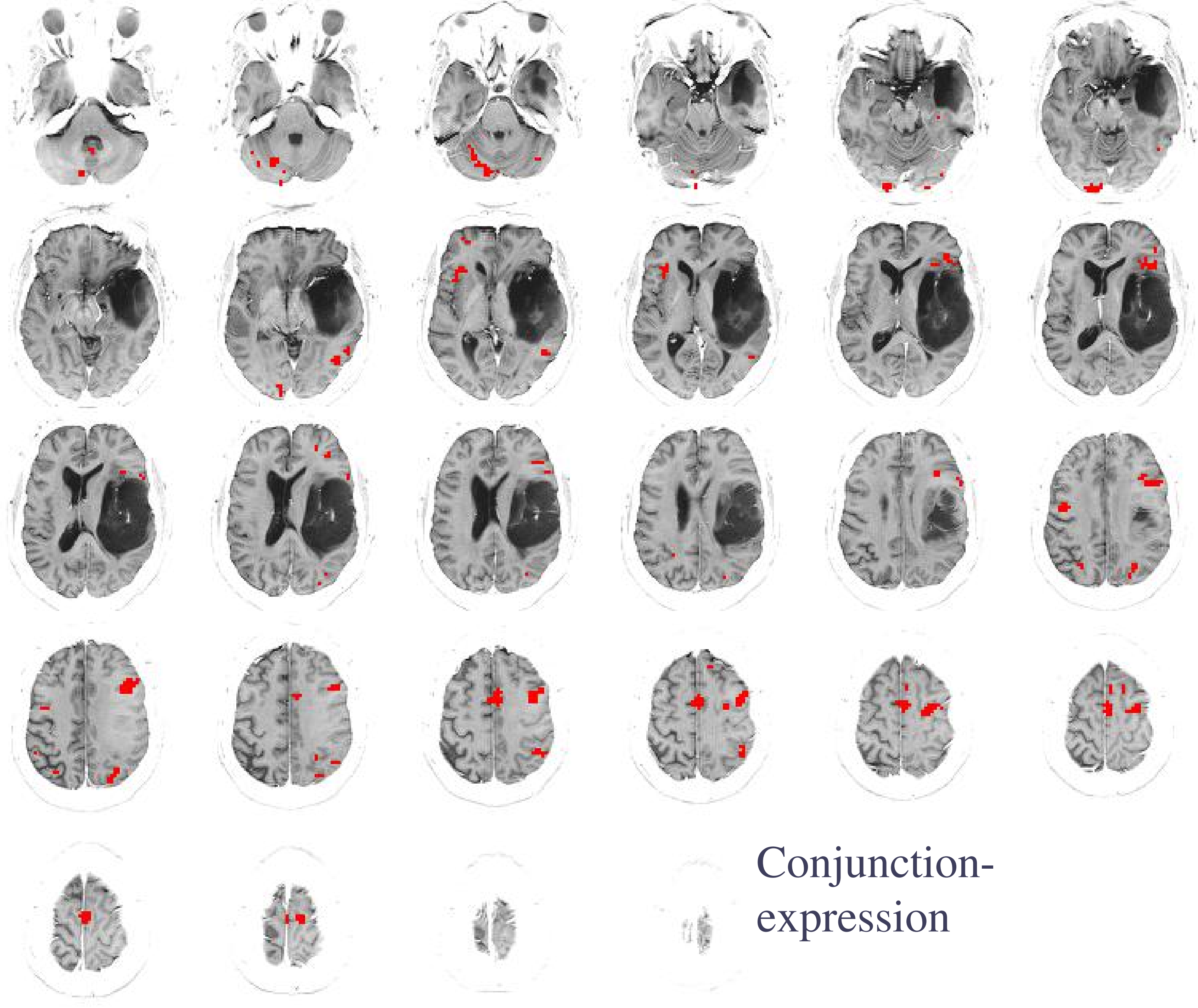
Object naming



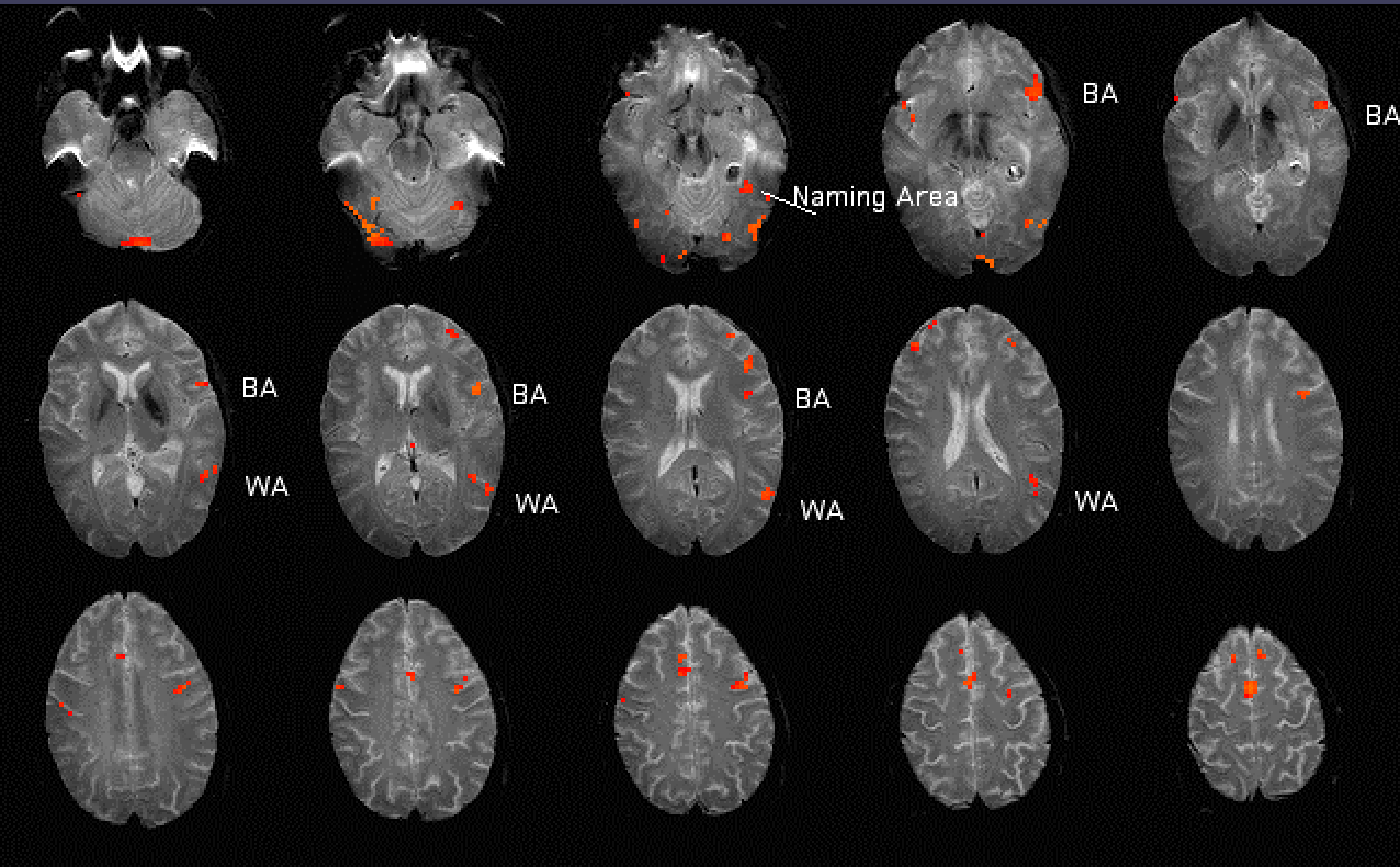
Reading comprehension with naming



Conjunction-
comprehension



Conjunction-
expression

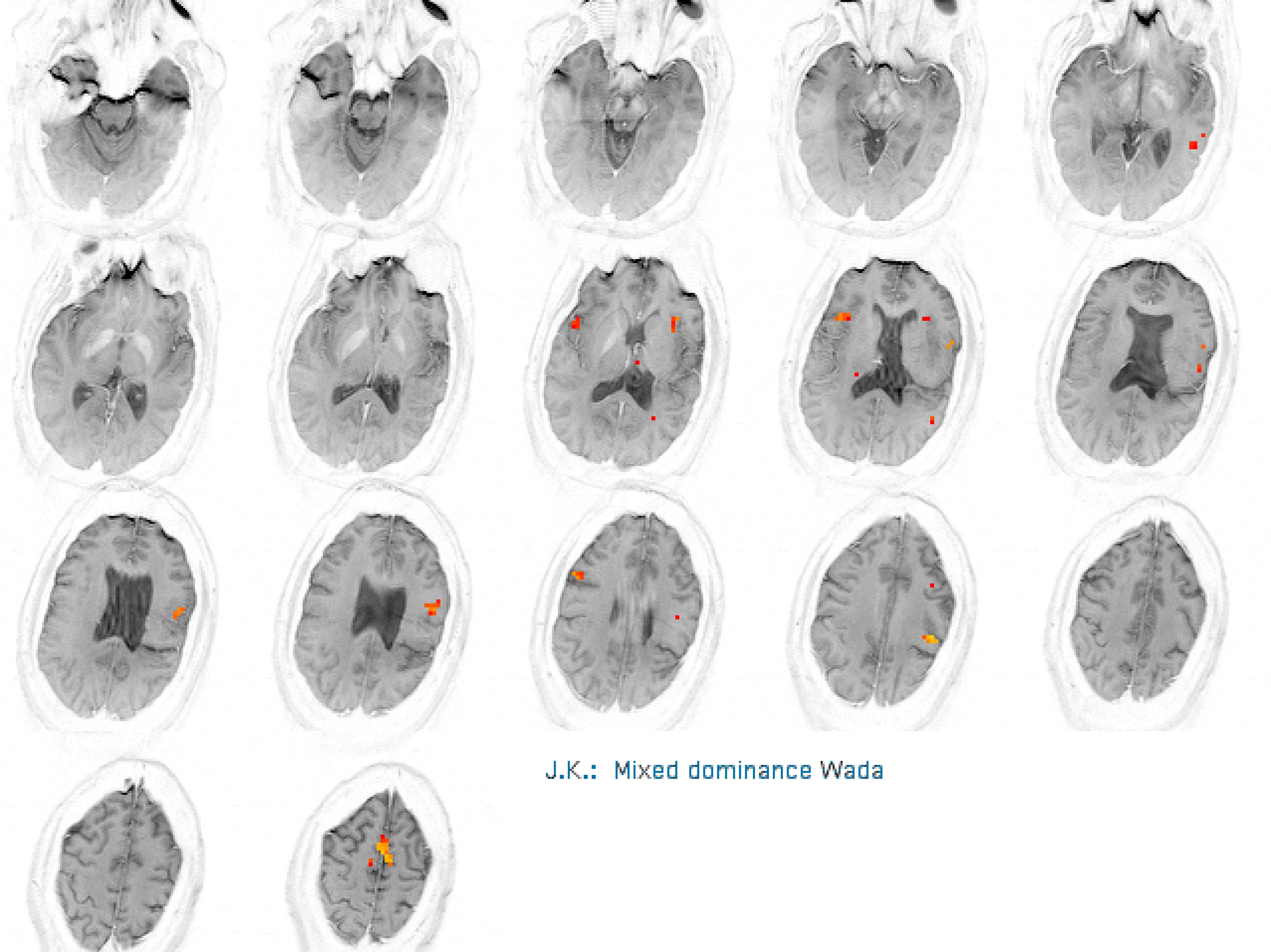

BA
BA
Naming Area
BA
BA
BA
WA
WA
WA
WA

Base rates and laterality

- Left hemisphere dominance (LBS): 99+ % right handers; 33-66% left handers; RBS about 33% left handers
- Mixed dominance; about 33% of left handers: does NOT imply equipotentiality; anterior left, posterior right, or reverse
- Nature/ age of onset of the lesion, handedness, and family history of handedness all modify the base rates
- RH, Adult onset lesion (tumor, head injury)- RBS is shockingly rare
- Childhood onset lesion with intact RH- > p of RBS. Epilepsy; AVM; perinatal stroke

Laterality, cont.

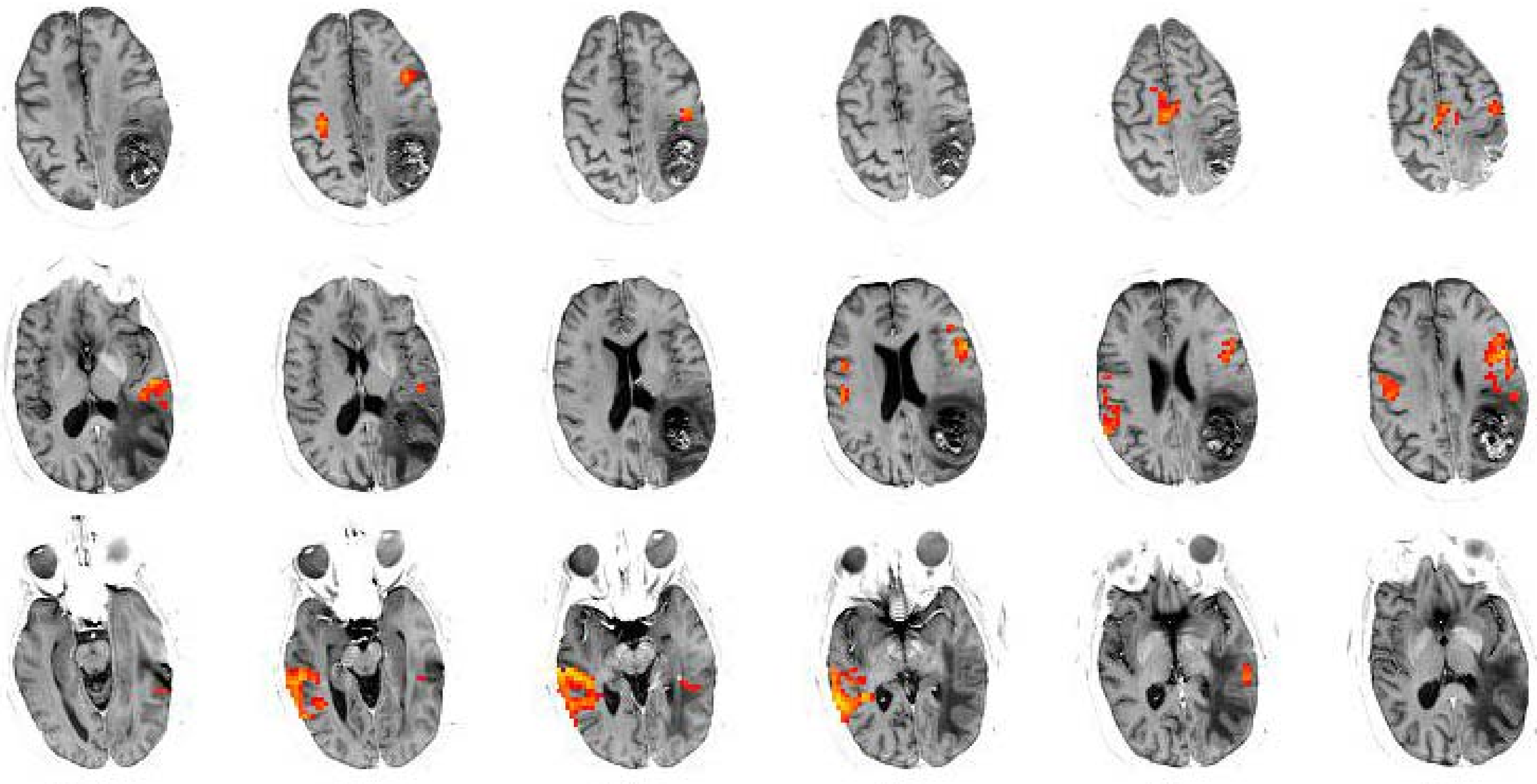
- Task “panel” approach superior: look for consistencies across different language tasks; at least 3
- Only use tasks relevant for your specific question:
  - don’t use word generation to measure receptive speech dominance
- Never calculate LI if the data are not pristine
  - Head motion, other artifacts
  - If signal is reduced due to other factors (edema, susceptibility artifacts, etc
- Always take into account base rates before you interpret the data



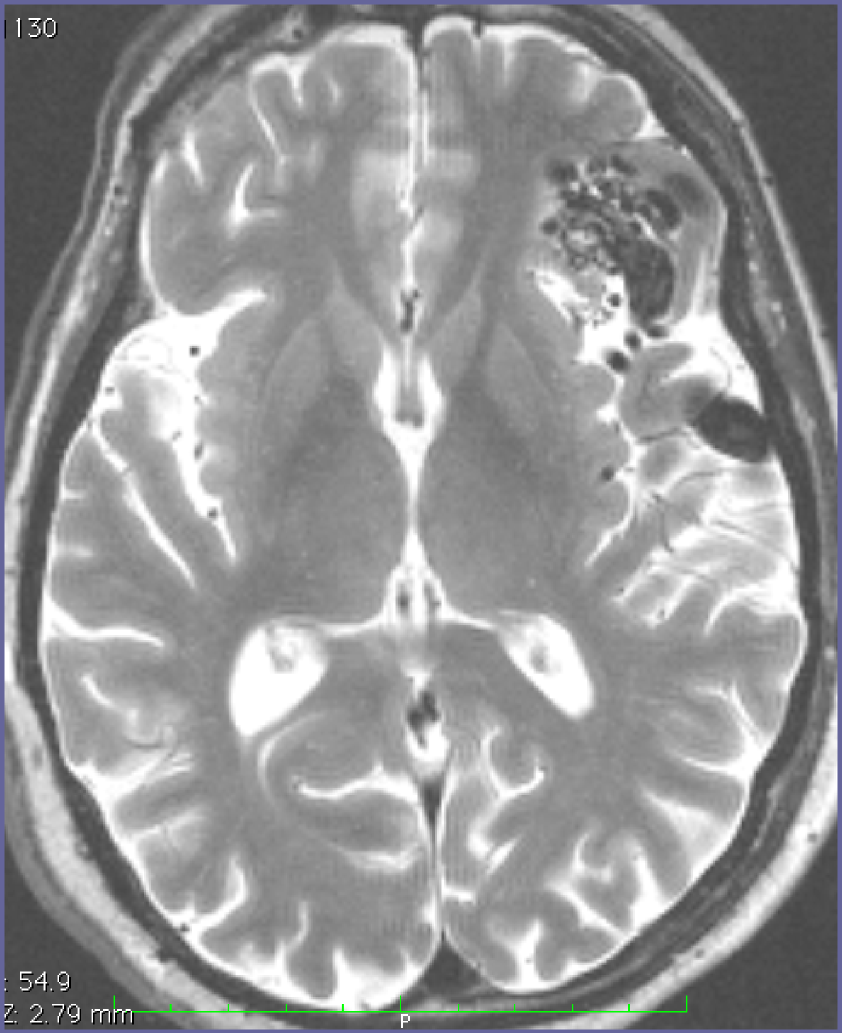
J.K.: Mixed dominance Wada

Lesions affect blood flow

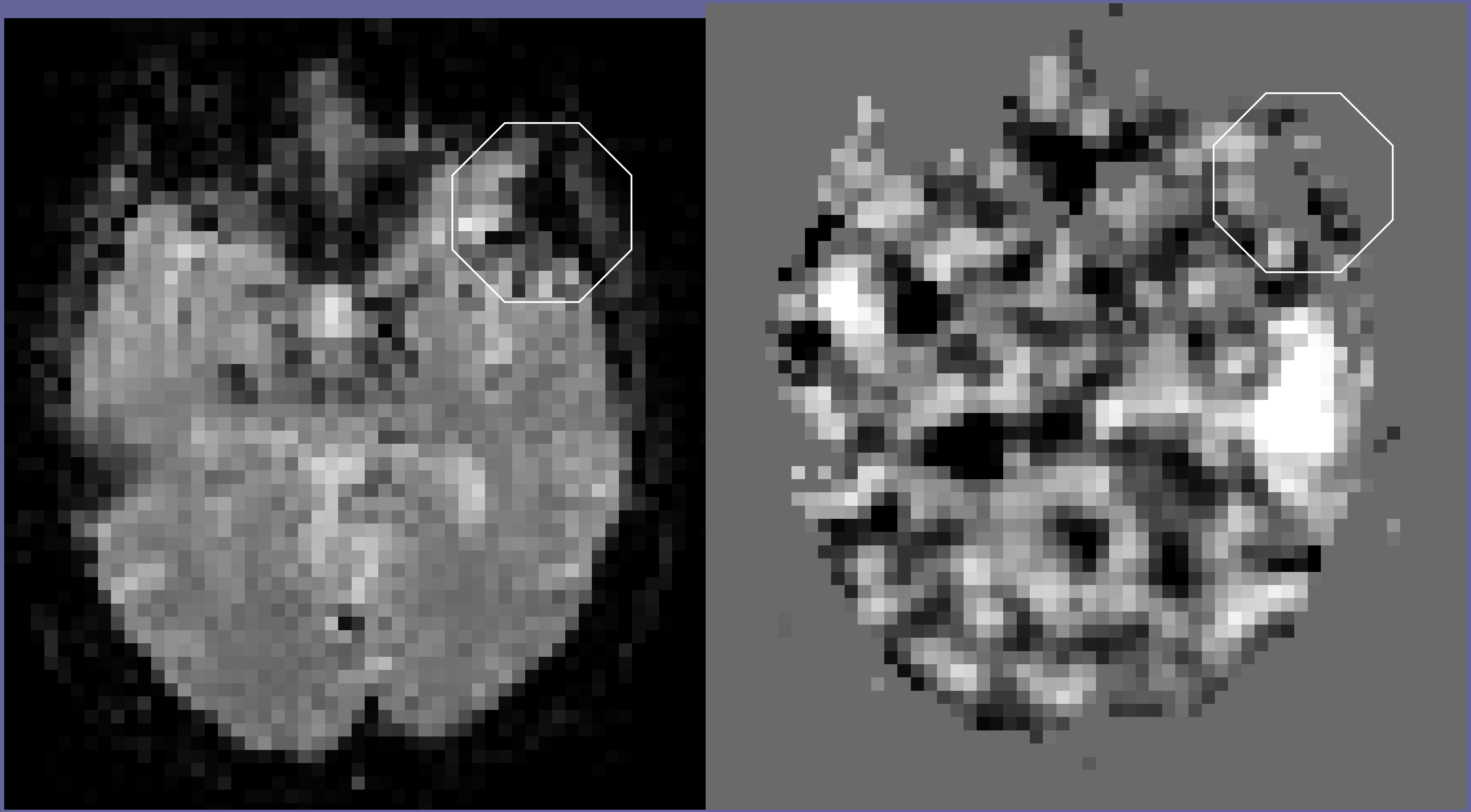
-



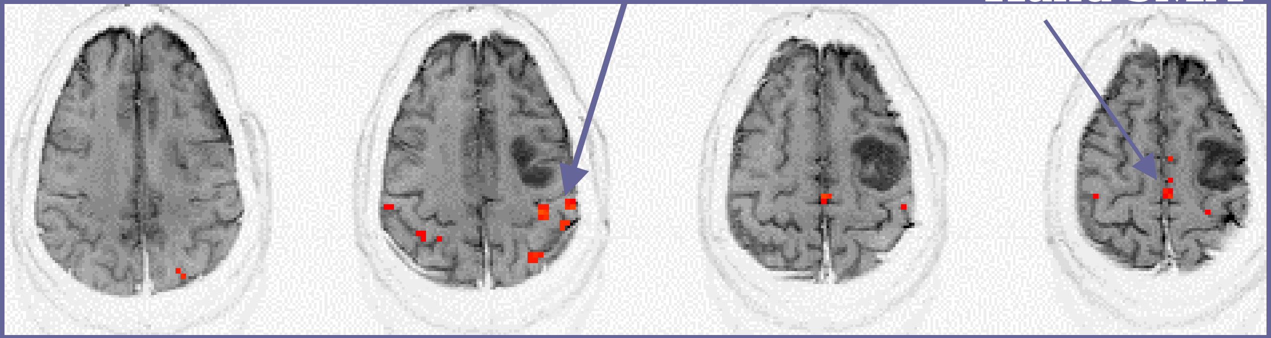
AVM

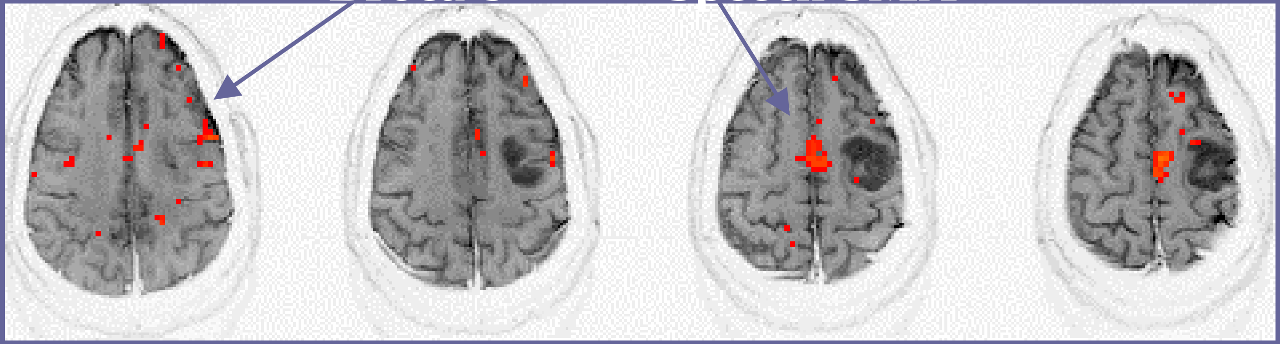


AVM induced signal loss



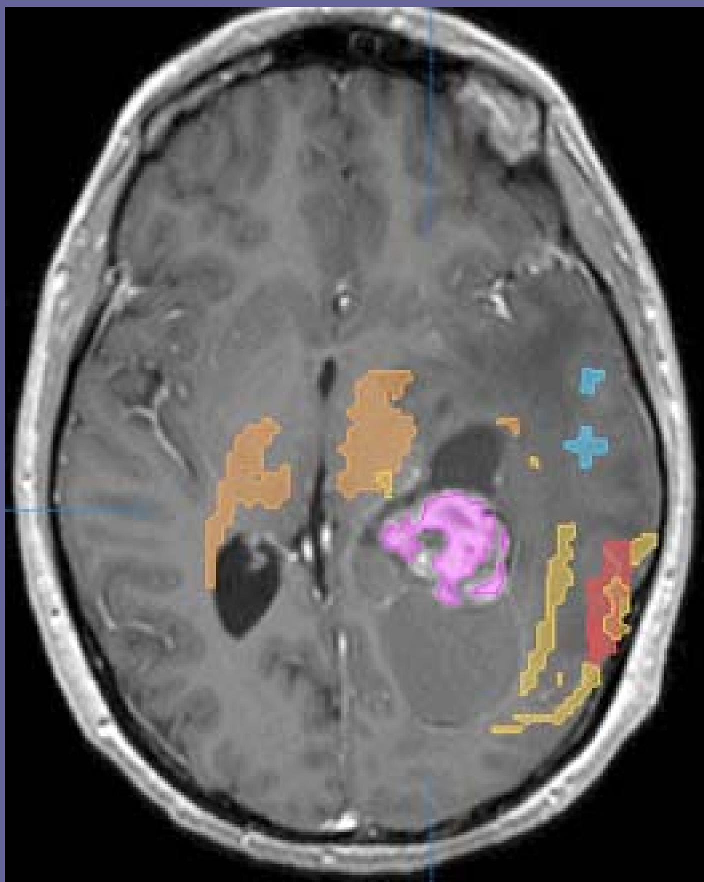
White matter disruption

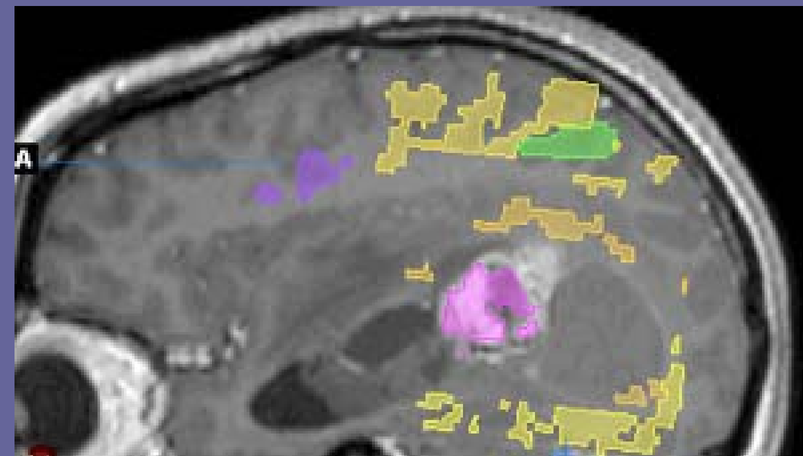


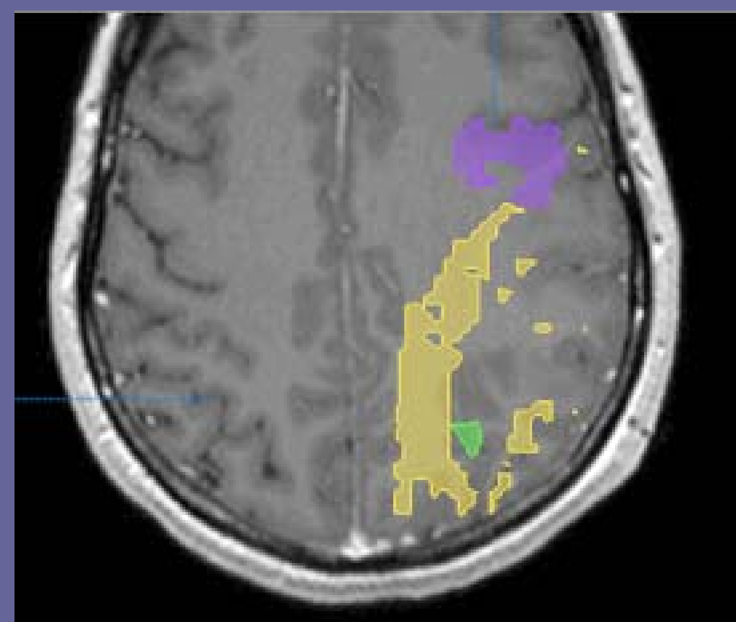


Post-operative expressive aphasia
Rapid recovery (2 weeks to normal)

Add DTI







Summary

- Especially for language mapping, fMRI is very complex.
- Close contact with the raw data, and with the patient's status (including presence of deficits, history of lesion, handedness, etc) is essential to avoid errors
- Validation of your local approach with traditional methods (Wada testing, cortical stimulation mapping) is essential

Multi-channel MRI at ultra-low fields compatible with MEG

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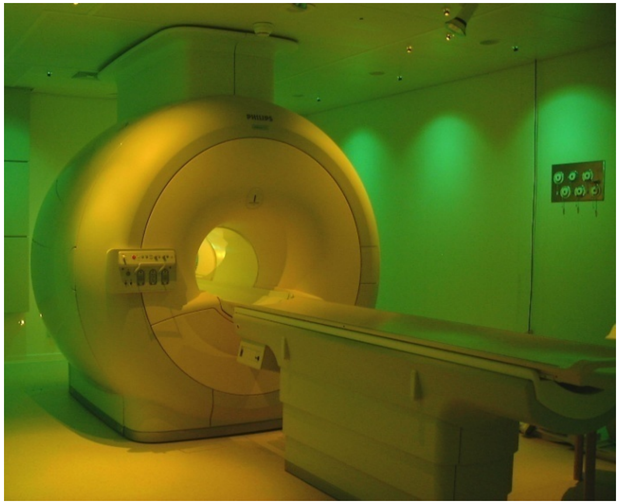
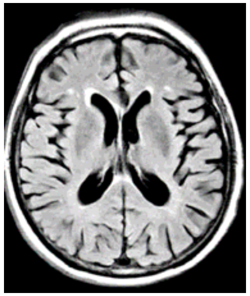
Outline

- *Introduction*
- *Instrumentation for ULF MRI*
- *3D imaging of a human hand*
- *3D imaging of a sheep brain*
- *Accelerated imaging*
- *Magnetoencephalography*
- *Conclusions*

Introduction

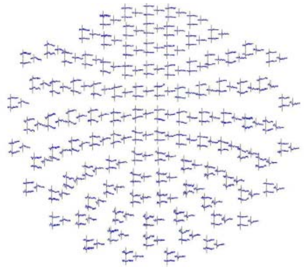
Magnetic resonance imaging (MRI)





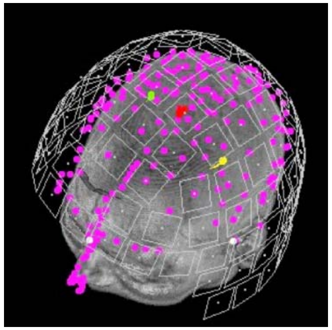
Philips Achieva
3 Tesla MRI
scanner

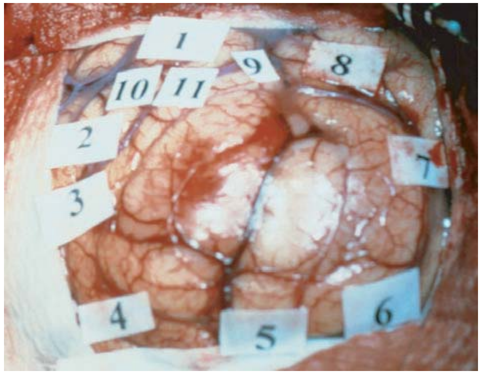
Magnetoencephalography (MEG)



Elekta Neuromag
306-chan MEG
system

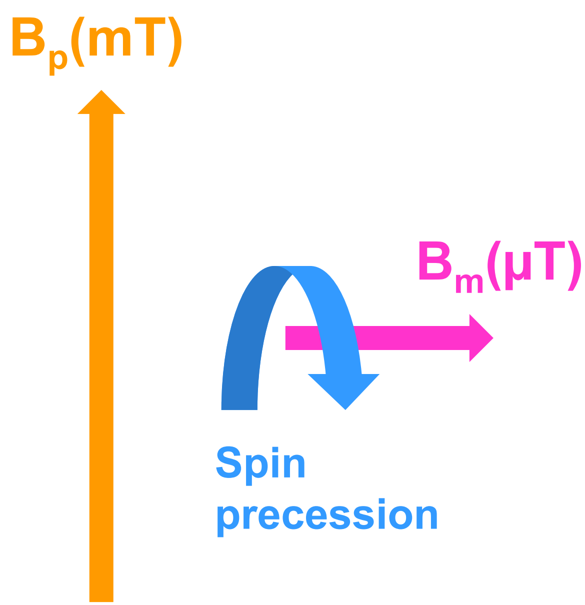
Co-registration of MEG and MRI data

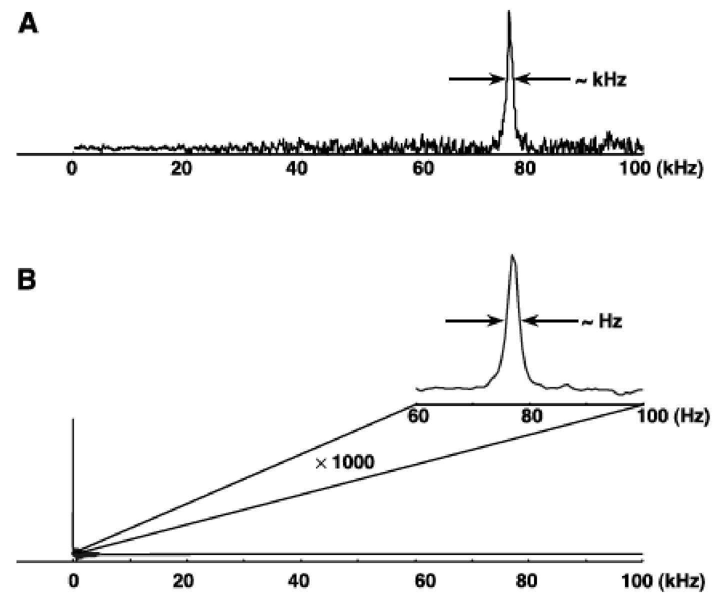




Co-registration errors are 5-10 mm !

<u>Magnetic resonance imaging at ultra-low fields</u> (ULF MRI) is a new imaging approach that uses SQUIDs to measure the spatially encoded spin precession at microtesla-range measurement fields





$\omega=\gamma|\mathbf{B}|$, $\gamma/2\pi=42.6$ Hz/μT
NMR line broadening:
$\delta\omega=\gamma\delta B=\gamma(\delta B/B)B$

Reference: R. McDermott *et al*. Liquid-state NMR and scalar couplings in microtesla magnetic fields. *Science* 295, p.2247 (2002).

Reference: R. McDermott *et al*. Microtesla MRI with a superconducting quantum interference device. *PNAS* 101, p.7857 (2004).

Objectives of our work:

- *Investigate the potential of multi-sensor ULF MRI, particularly for human brain imaging.*
- *Combine ULF MRI and magnetoencephalography (MEG) in one multi-channel instrument.*

Benefits for neuroimaging:

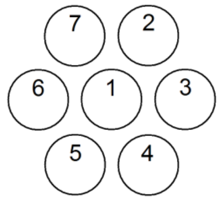
- *Elimination of MEG/MRI co-registration errors*
- *Simultaneous functional (MEG) and anatomical (ULF MRI) imaging of the human brain*

Reference: V.S. Zotev *et al*. Multi-channel SQUID system for MEG and ultra-low-field MRI. *IEEE Trans Appl Supercond* 17, p. 839 (2007).

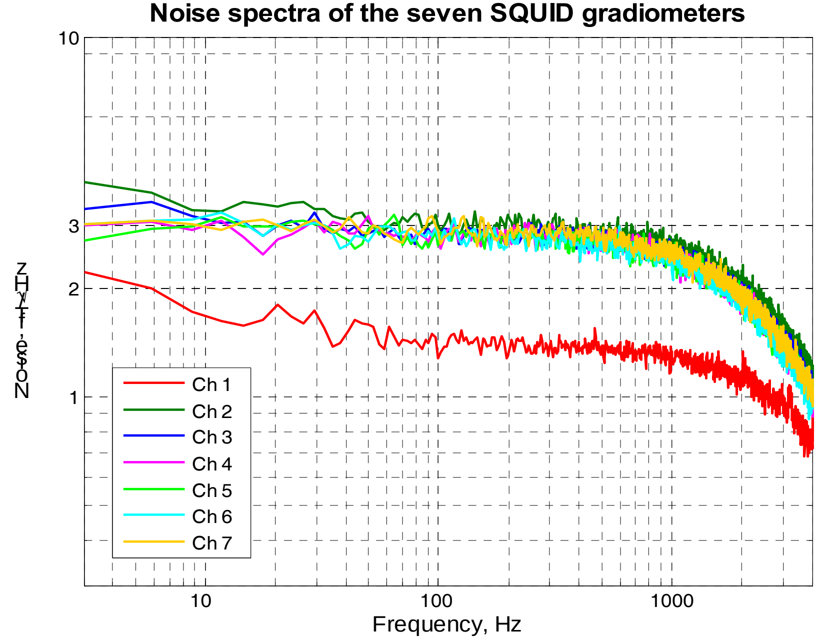
Reference: P. Volegov *et al*. Simultaneous magnetoencephalography and SQUID detected NMR in microtesla magnetic fields. *MRM* 52, p. 467 (2004).

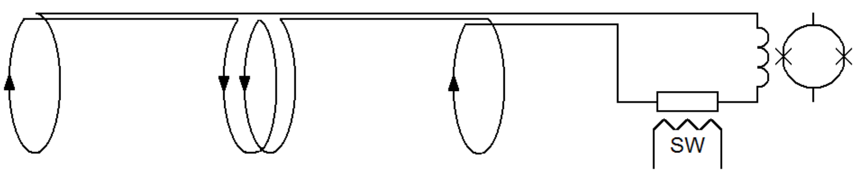
Instrumentation for ULF MRI

Seven gradiometers with SQUIDs



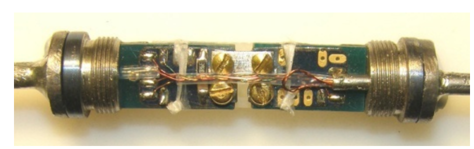
Gradiometers are second-order, with 37 mm diameter and 60 mm baseline. They are placed as shown above with 45 mm separations between nearby coil centers





SQUID flux noise: 5 $\mu\Phi_0\sqrt{\text{Hz}}$ for channel 1. Field resolution is ≈1.2 fT/√Hz at 1 kHz for the central channel (Ch 1) and ≈2.8 fT/√Hz for the surrounding channels (due to the dewar noise). The roll-off is a characteristic of the DAQ used.

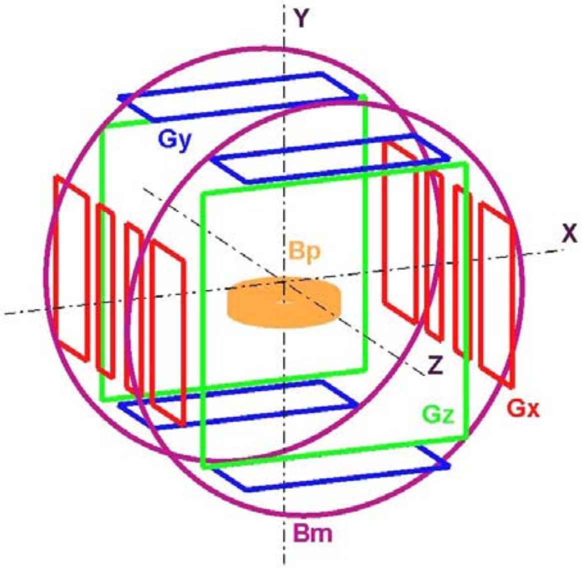
The cryoswitch protects the SQUID from transients caused by strong Bp pulses. It becomes resistive when its heater is activated. Switching time: < 5 µs, ON resistance: 50 ohm



SQUID ‘CE2 blue’ (left) and cryoswitch ‘SW1’ (right) from Supracon AG, Jena,Germany

General view of the system

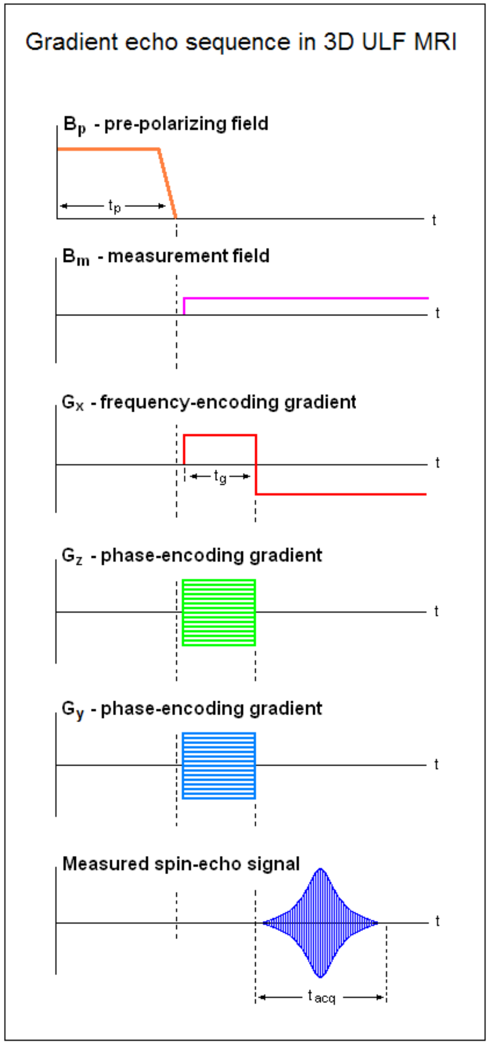
Schematic of the coil system



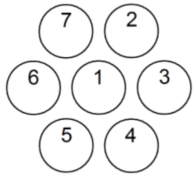
Pre-polarizing field: B_p = 40-50 mT
Measurement field: B_m = 46 µT
The two fields are orthogonal and separated in time

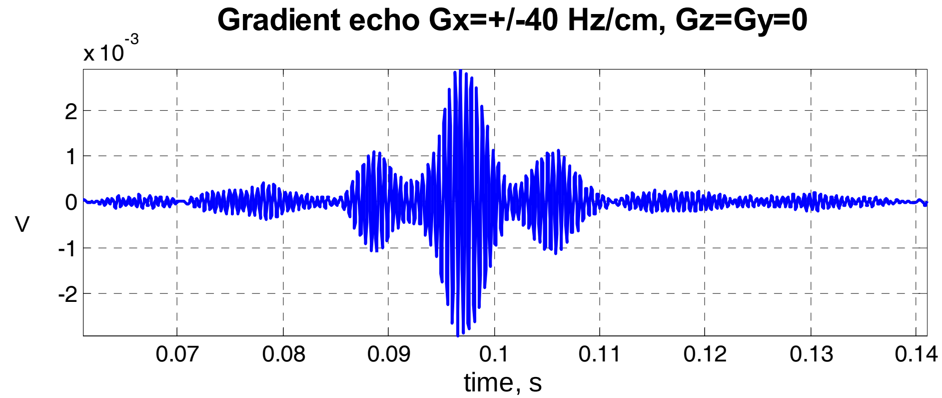
Gradients for 3D Fourier MRI:
$G_z=dB_z/dz$, $G_x=dB_z/dx$, $G_y=dB_z/dy$

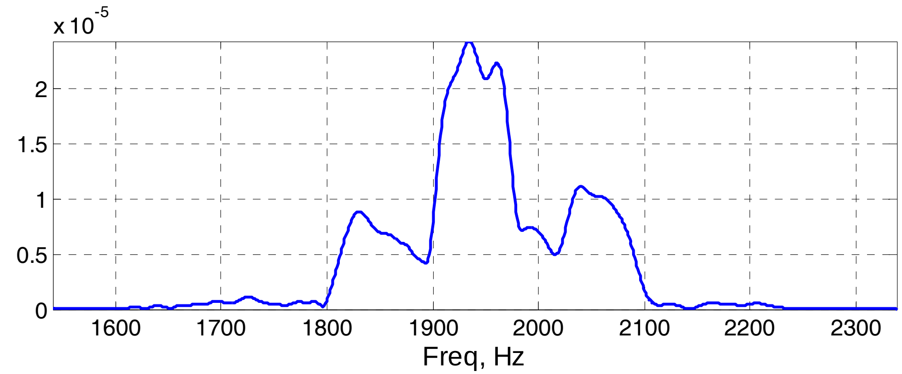
Imaging protocol



3D imaging of a human hand







Imaging parameters

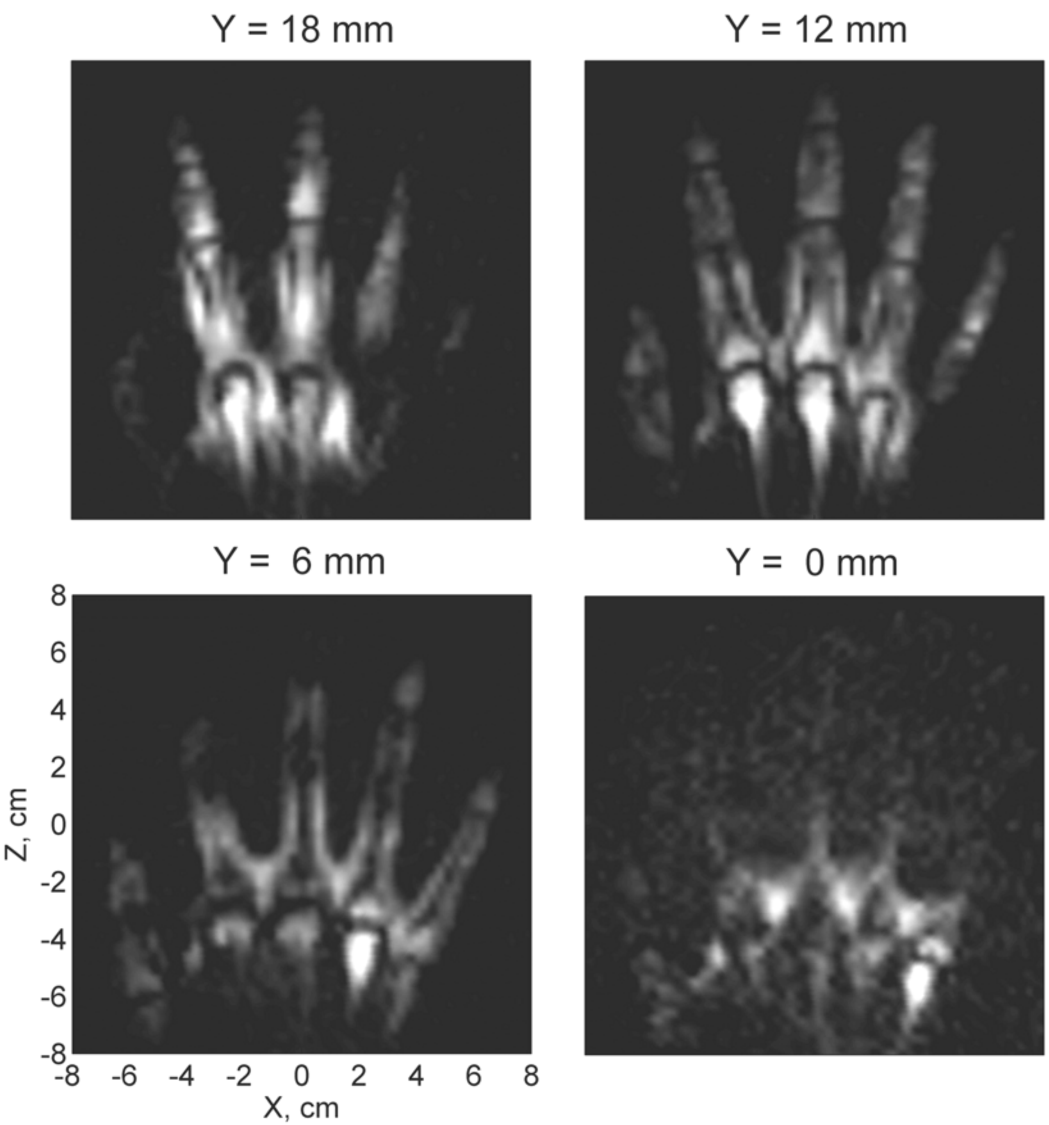
Pre-polarization time: t_p = 0.5 s
Encoding time: t_g = 42 ms
Acquisition time: t_{acq} = 84 ms

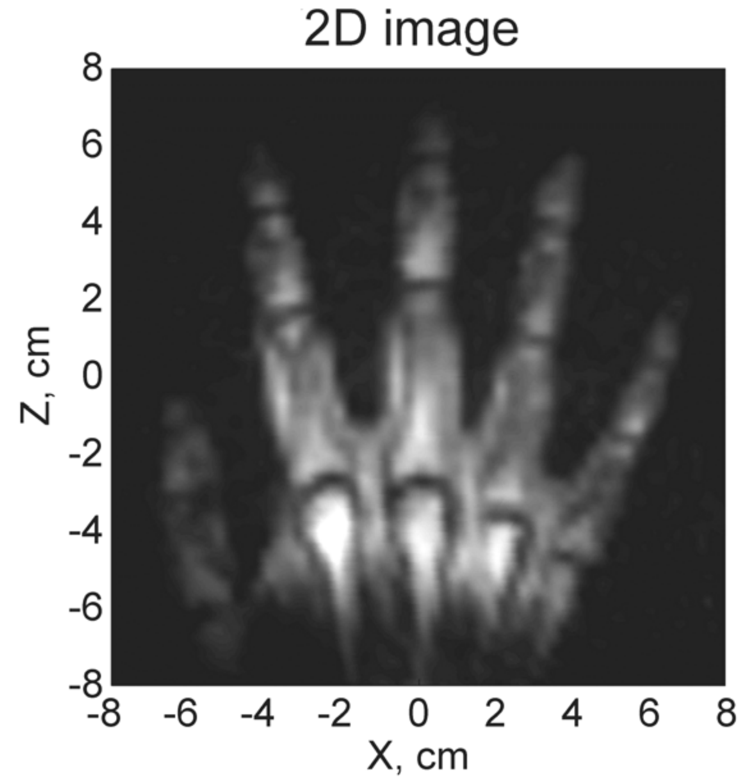
Pre-polarizing field: B_p = 40 mT
Measurement field: B_m = 46 μT (~1940 Hz)

Gradient echo: G_x = +/-40 Hz/cm
Phase encoding:
G_z = -40 Hz/cm…+40 Hz/cm, 55 steps
G_y = -20 Hz/cm…+20 Hz/cm, 9 steps

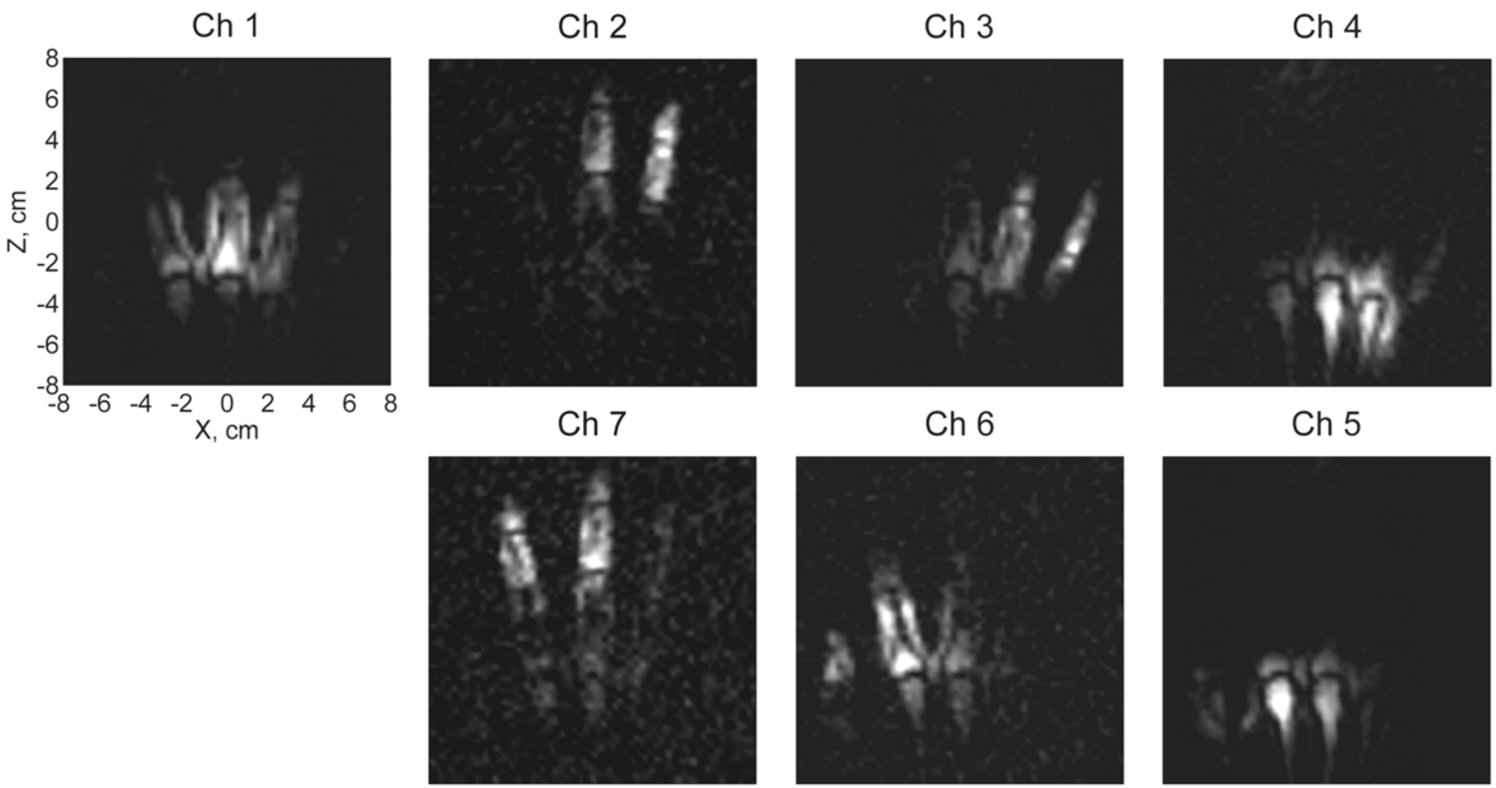
Imaging resolution: 3 mm × 3 mm × 6 mm
Number of scans averaged: 12
Total imaging time: ~1 hour

The mean relaxation time T_2 for the hand is ~120 ms


Y = 18 mm
Y = 12 mm
Y = 6 mm
Y = 0 mm
Z, cm
X, cm
8
6
4
2
0
-2
-4
-6
-8

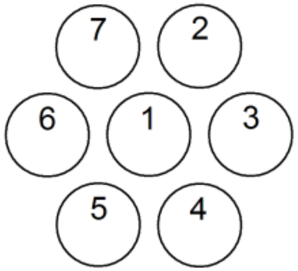

2D image
Z, cm
X, cm
8
6
4
2
0
-2
-4
-6
-8

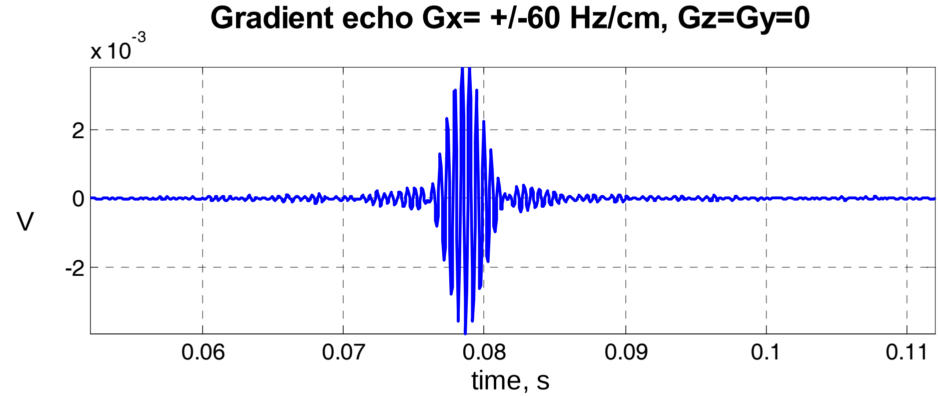
Images from the seven individual channels for *Y*=12 mm

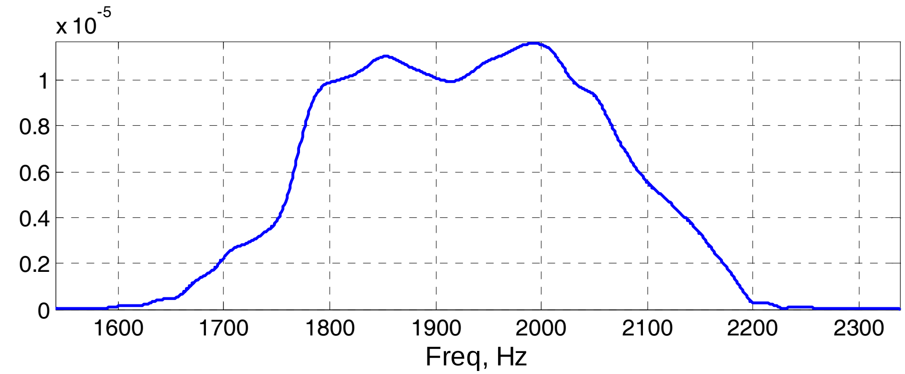


Sensor array expands FOV

3D imaging of a sheep brain







Imaging parameters

Pre-polarization time: t_p = 0.5 s
Encoding time: t_g = 33 ms
Acquisition time: t_{acq} = 66 ms

Pre-polarizing field: B_p = 40 mT
Measurement field: B_m = 46 μT (~1940 Hz)

Gradient echo: G_x = +/-60 Hz/cm
Phase encoding:
G_z = -60 Hz/cm…+60 Hz/cm, 33 steps
G_y = -30 Hz/cm…+30 Hz/cm, 11 steps

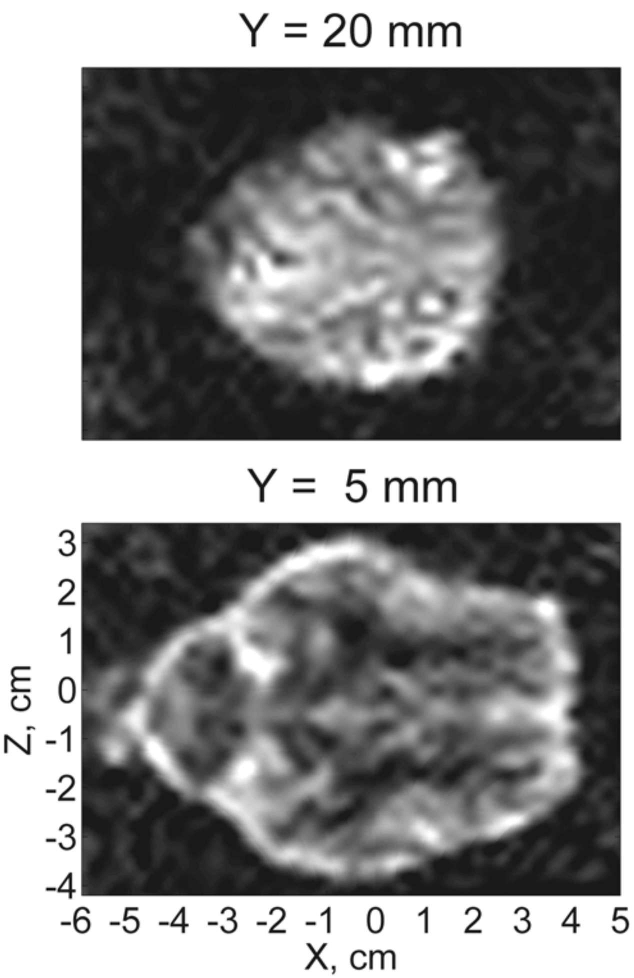
Imaging resolution: 2.5 mm × 2.5 mm × 5 mm
Number of scans averaged: 42
Total imaging time: ~3 hours

The sheep brain is preserved in formaldehyde.
The mean relaxation time T_2 is ~40 ms

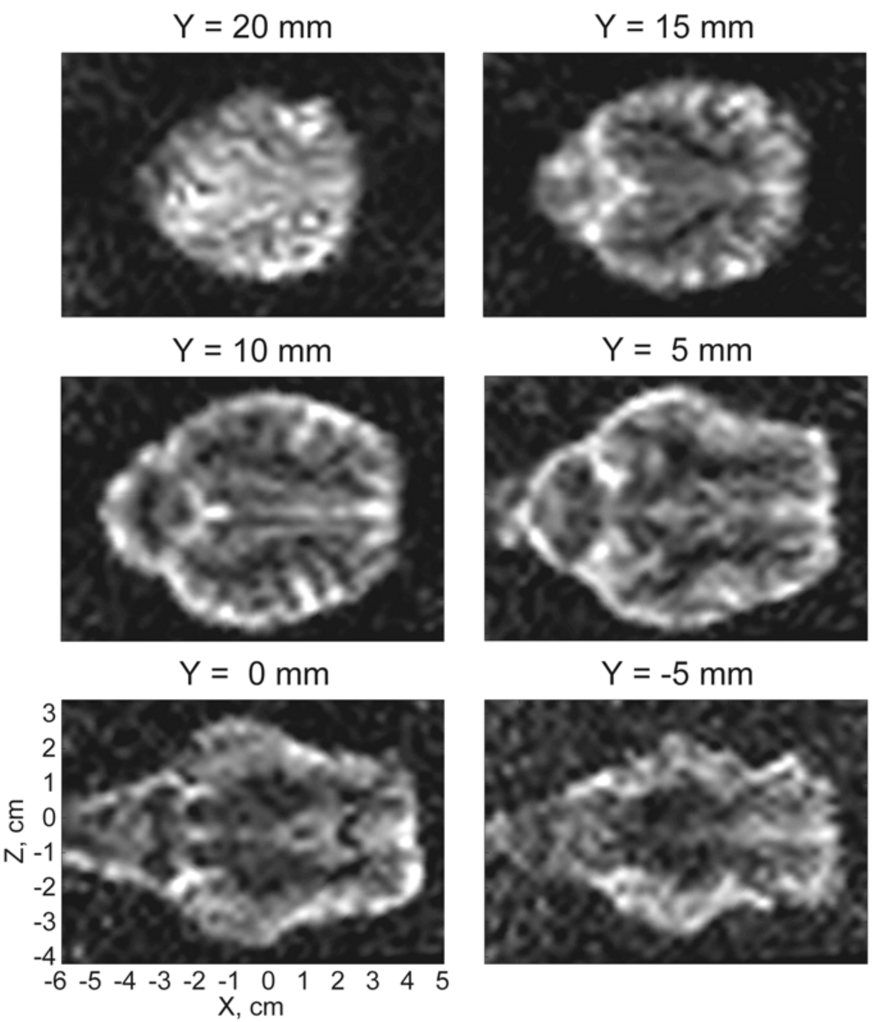
Imaging at high field

B=2 Tesla, TE=26 ms, TR=1500 ms
Slices are 2 mm thick, 5 mm apart
In-plane resolution: 1mm × 0.5 mm

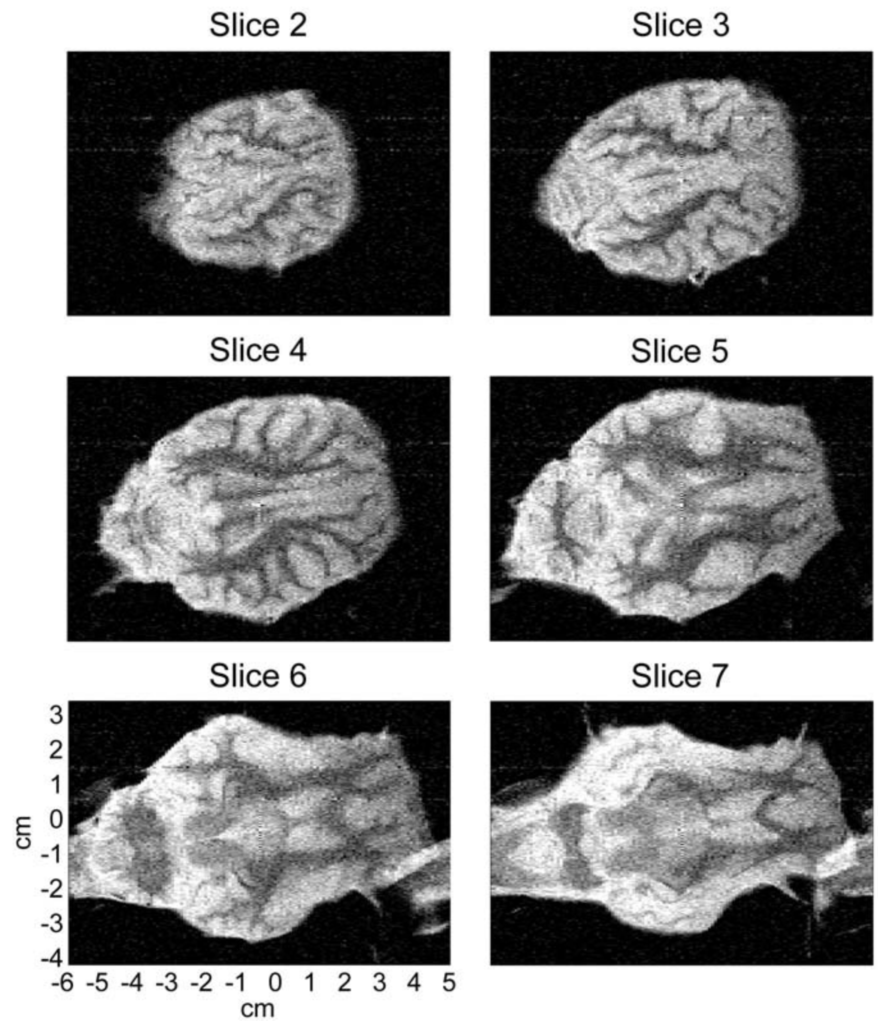
Composite seven-channel images of the sheep brain with sensitivity correction



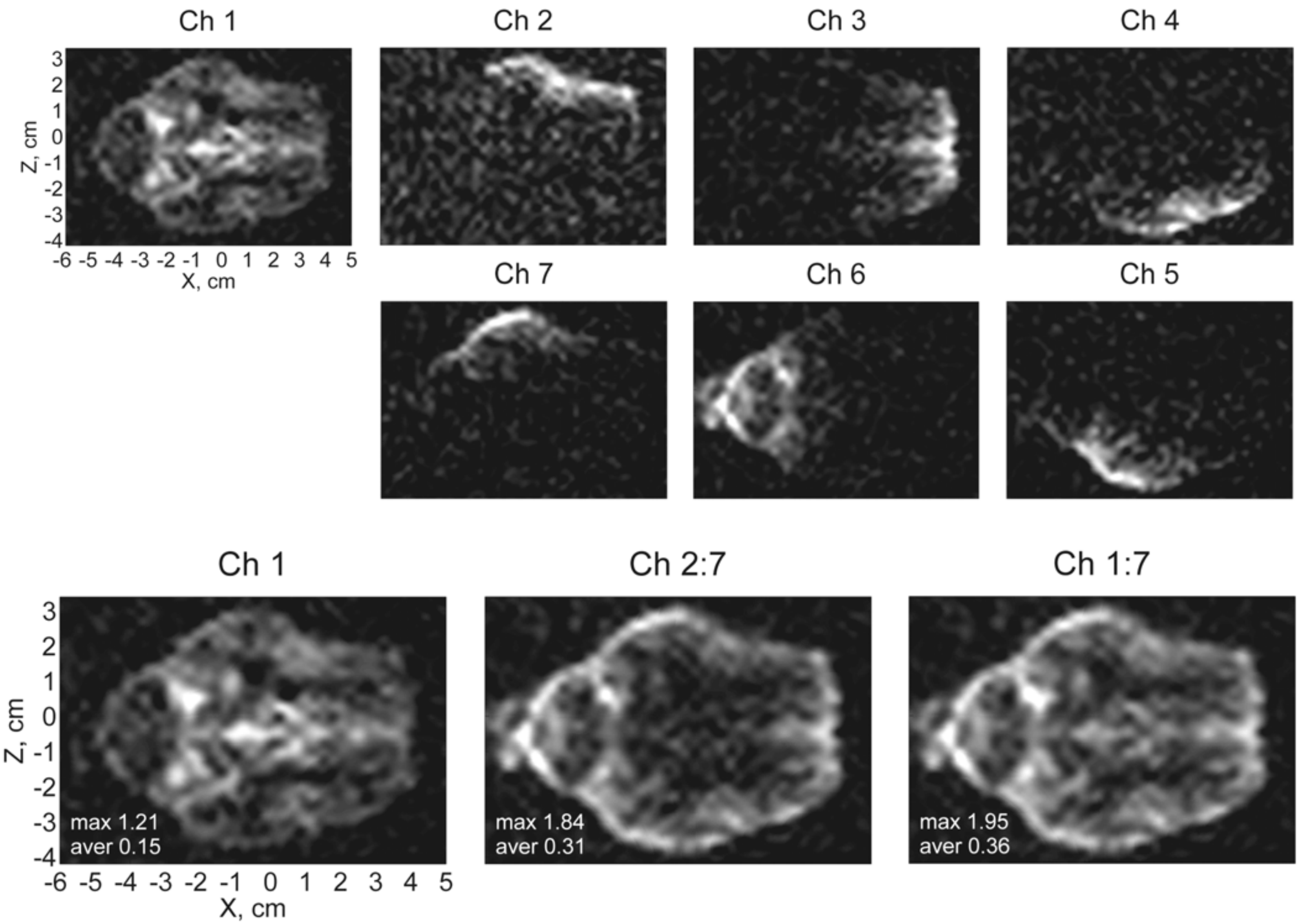
Images acquired at 46 μT



Images acquired at 2 Tesla

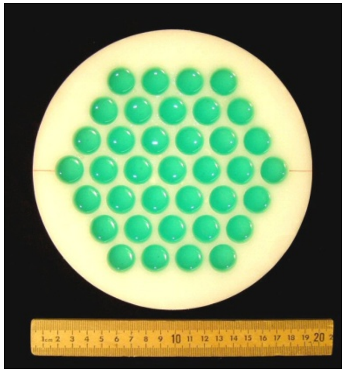


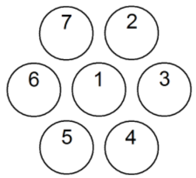
Images from the seven individual channels for *Y*=5 mm

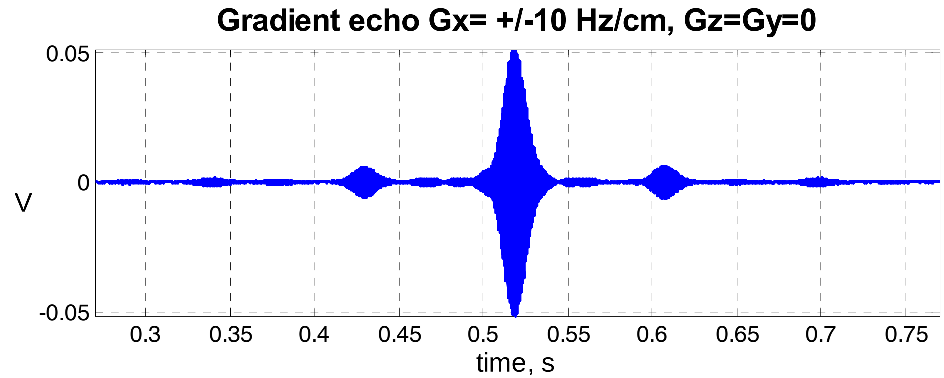


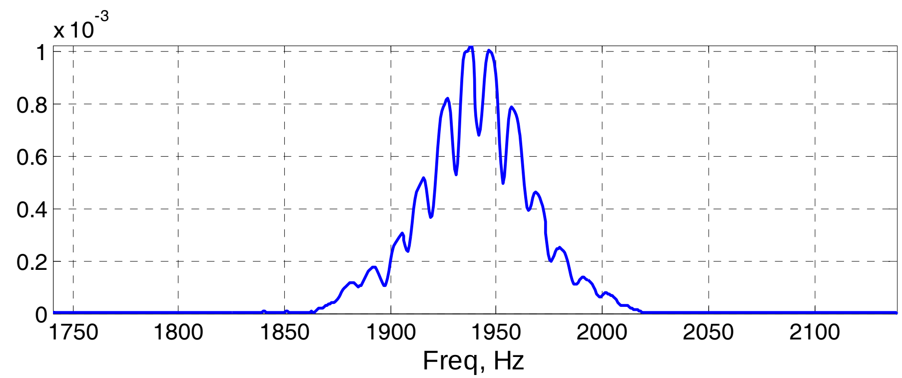
Sensor array improves SNR

Accelerated imaging









Imaging parameters

Pre-polarization time: t_p = 4 s
Encoding time: t_g = 250 ms
Acquisition time: t_{acq} = 500 ms

Pre-polarizing field: B_p = 50 mT
Measurement field: B_m = 46 µT (~1940 Hz)

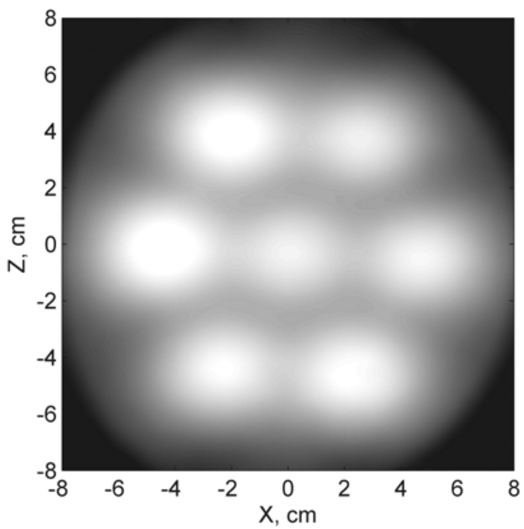
Gradient echo: G_x = +/-10 Hz/cm
Phase encoding:
G_z = -10 Hz/cm…+10 Hz/cm, 73 steps

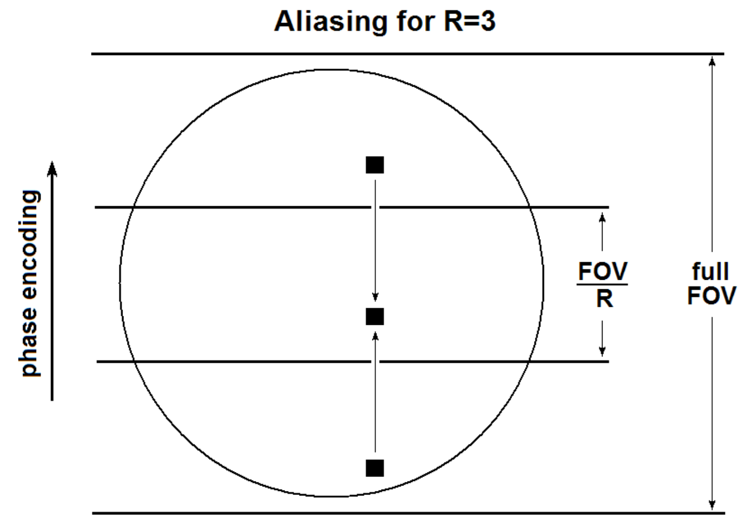
Imaging resolution: 2 mm × 2 mm
Number of scans averaged: 1
Imaging time for full FOV: ~6 min

The phantom holes are filled with water (colored in the picture).They are 19 mm in diameter, 19 mm deep, and have 22 mm center-to-center spacing.

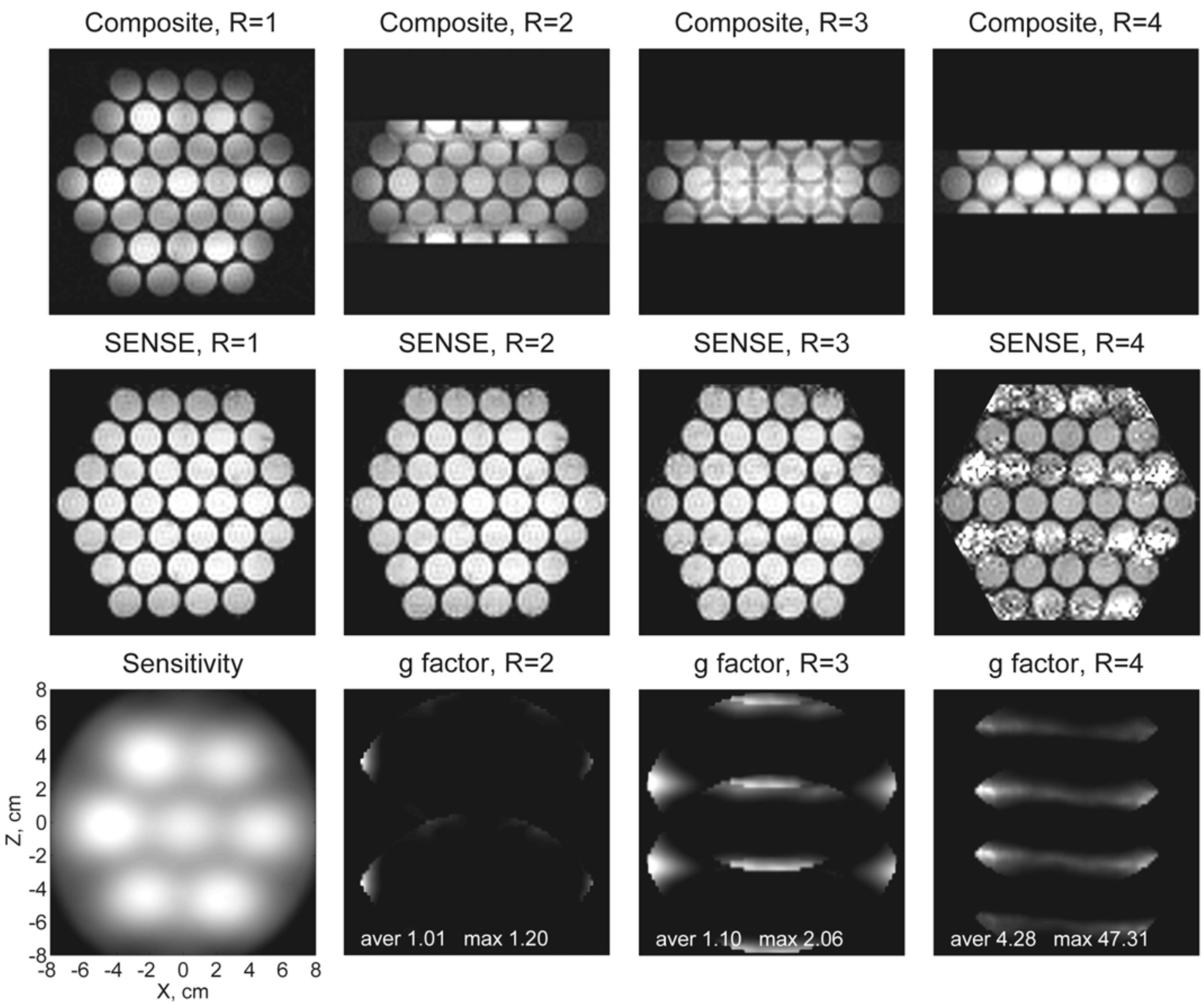
Accelerated imaging by sensor array

- The number of phase encoding lines is reduced by factor R through R-fold increase in gradient step with the maximum gradient value (and imaging resolution) unchanged.
- The imaging FOV along the phase encoding direction is thus reduced R times, and aliasing occurs, i.e. each pixel in the reduced FOV is a superposition of up to R equidistant pixels in the full FOV.
- SENSE method: because the superposition of pixels occurs with different weights for different sensors, the aliased images can be 'unfolded' to produce a correct full-FOV image.





Reference: K.P. Pruessmann *et al*. SENSE: Sensitivity encoding for fast MRI. *MRM* 42, p.959 (1999).



R=1: 73 phase encoding lines acquired in **6 min**

R=2: 37 phase encoding lines acquired in **3 min**

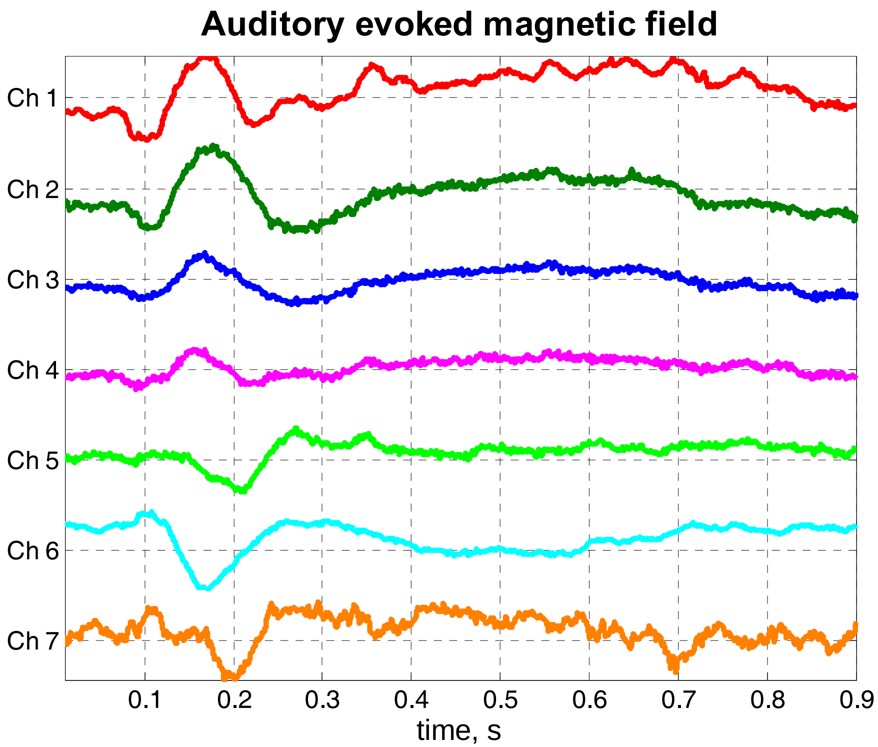
R=3: 25 phase encoding lines acquired in **2 min**

R=4: 19 phase encoding lines acquired in **1.5 min**

***Real* imaging acceleration in comparison to single-shot full-FOV imaging**

Los Alamos
NATIONAL LABORATORY
EST. 1943

MEG measurements



Auditory stimulus: train of 1.2 ms clicks with 14 ms intervals. Pre-stimulus interval: 50 ms

Polarities of the signals are consistent with the expected orientation of the equivalent current dipole perpendicular to the Sylvian fissure.

Conclusions

- *ULF MRI can potentially compete with high-field MRI.*
- *Imaging speed is limited mainly by the strength of the pre-polarizing field available and can be improved.*
- *Multiple sensors make it possible to increase image quality and/or imaging speed.*
- *New MEG instruments should be designed to include ULF MRI capability.*

We gratefully acknowledge support from U.S. NIH and from LANS, LLC for NNSA of U.S. DOE under LDRD.

Application of Atomic Magnetometer to MEG and NMR

Igor Savukov

Los Alamos National Laboratory

Princeton University

Contributors: Michael Romalis and Kiwoong Kim, Princeton University

Acknowledgement

SQUID team at Los Alamos

- Robert Kraus, Jr.
- Michelle Espy
- Andrei Matlachov
- Petr Volegov
- John Mosher
- Vadim Zotev

Princeton University

- Michael Romalis
- Kiwoong Kim
- H. Xia
- A. Ben-Amar Baranga
- Tom Kornack

Advantages of atomic magnetometers

- High sensitivity, exceeding SQUID's
- Non-cryogenic operation
- Low cost of multi-channel operation
- Portability
- Maintenance free operation
- Low field NMR/MRI
- No problems with rf noise
- Possibility to tune by external field
- Simultaneous MEG and MRI
- Direct neural imaging with ULF-MRI

There are some problems, though: sensitivity to vibrations, requirement for heating to 180C, limited bandwidth, residual DC field effects

Direct neural imaging

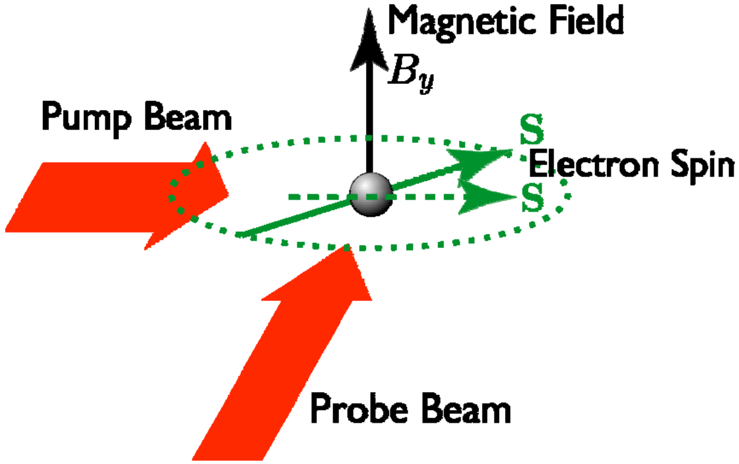
Idea – neural fields can affect locally NMR signals

- Spatial resolution is similar to MRI
- No ambiguity of MEG
- Neural activity (functional) information
- Fast time resolution, unlike fMRI

Los Alamos group works on theoretical modeling of neural fields: of a single neuron and a network of neurons

Los Alamos group conducted some preliminary phantom experiment using ULF-NMR system

SERF magnetometer



SERF – spin-exchange relaxation free,
Analog motional narrowing in NMR

Spin shot noise

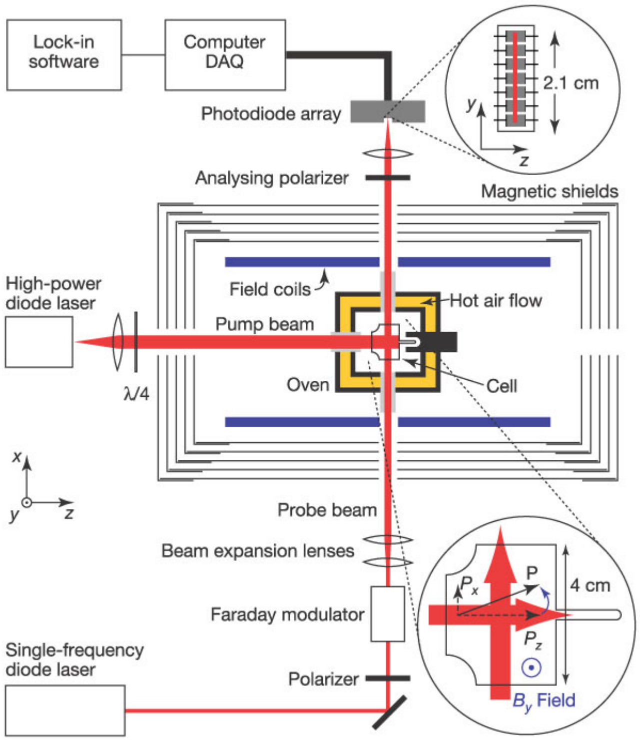
$$\delta B = \frac{1}{\gamma\sqrt{nT_2Vt}}$$

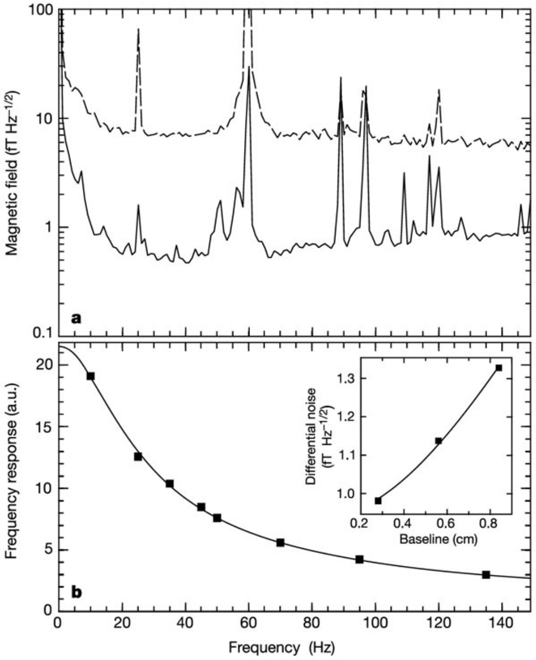
The width in SERF regime
is 1-2 Hz

$$\delta B = 10^{-17}\, T V^{-3/2} Hz^{-1/2}$$

J. Allred, R. Lyman, T. Kornack, M. Romalis, "A high-sensitivity atomic magnetometer unaffected by spin-exchange relaxation." *Phys. Rev. Lett.* **89**, 130801 (2002).

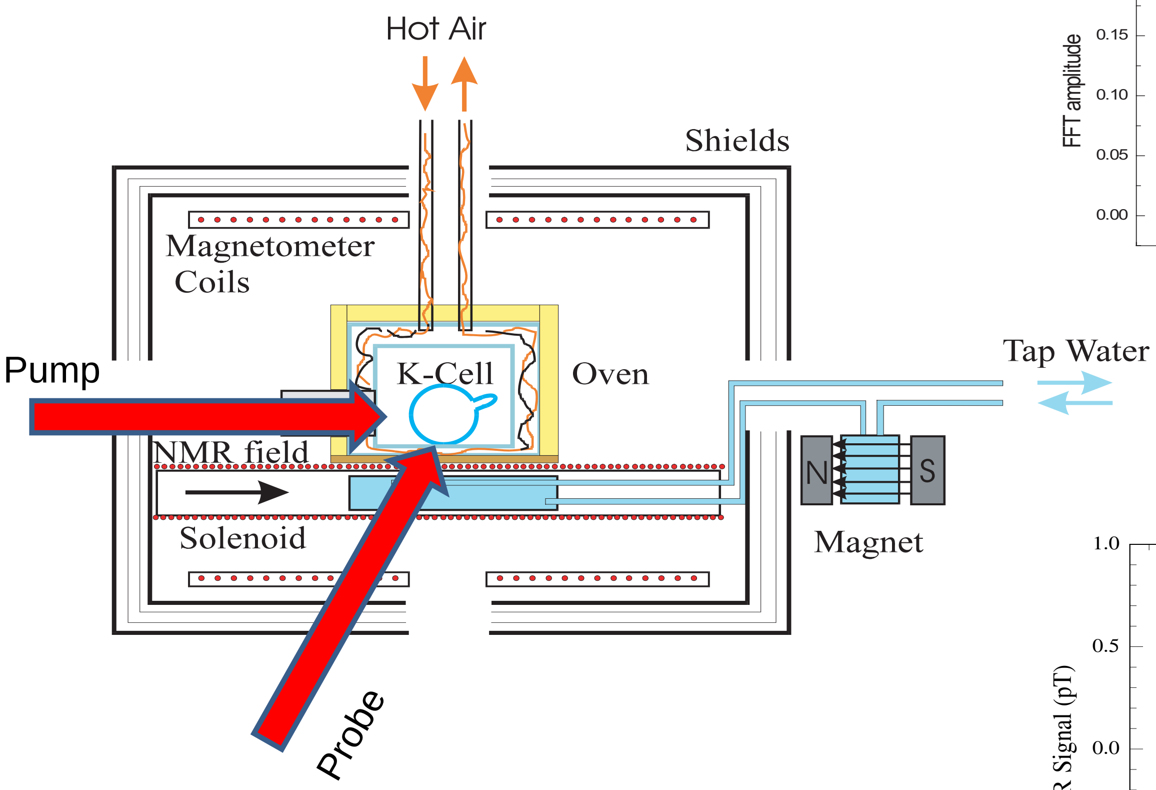
Most sensitive magnetometer

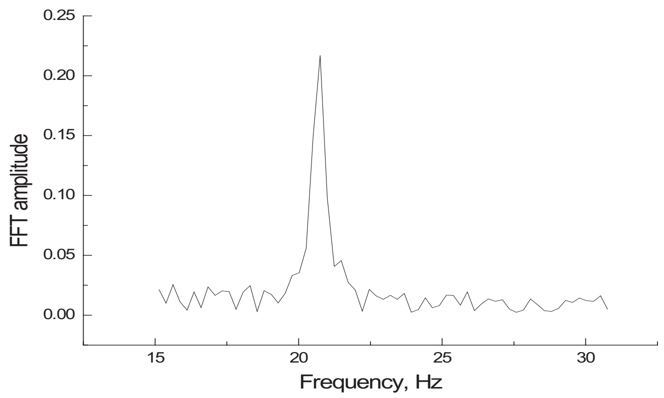


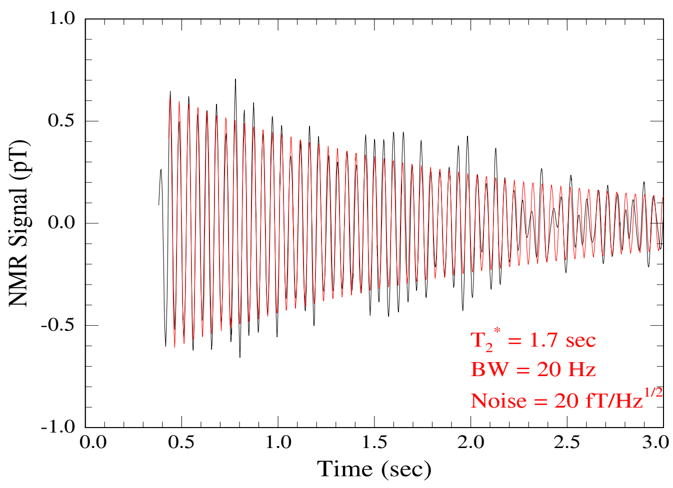


[A subfemtotesla multichannel atomic magnetometer]
I. K. Kominis, T. W. Kornack, J. C. Allred and M. V. Romalis
Nature 422, 596-599(2003)

20 Hz NMR with SERF

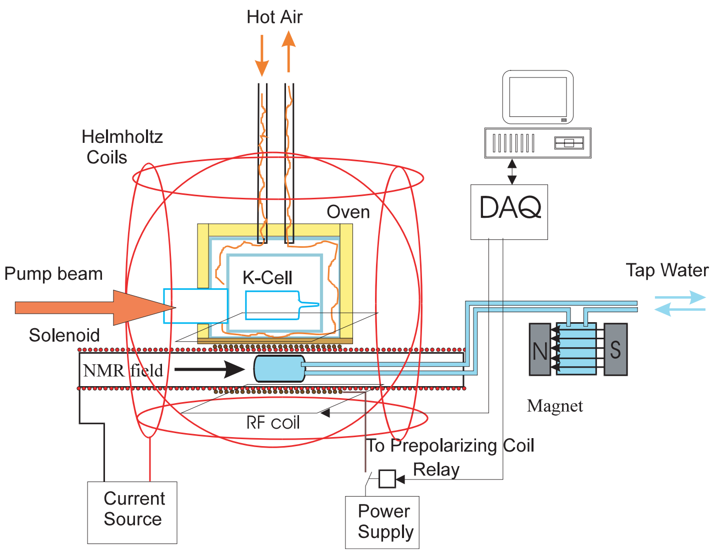


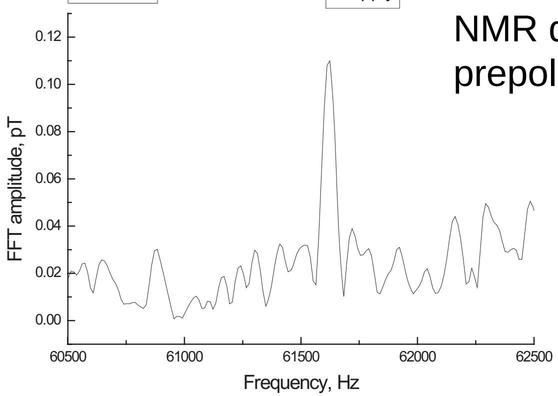




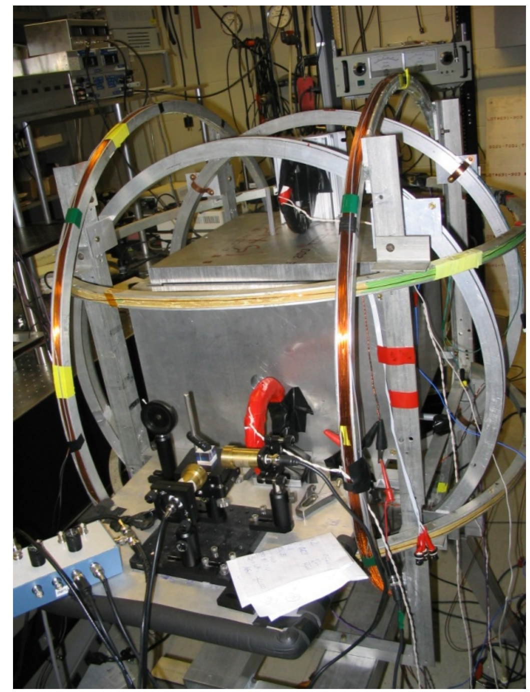
I. M. Savukov and M. V. Romalis. "NMR Detection with an Atomic Magnetometer." *Phys. Rev. Lett.* **94**, 123001 (2005).

NMR detection with RF atomic magnetometer





NMR detection, prepolarization 100 G



Aluminum shield

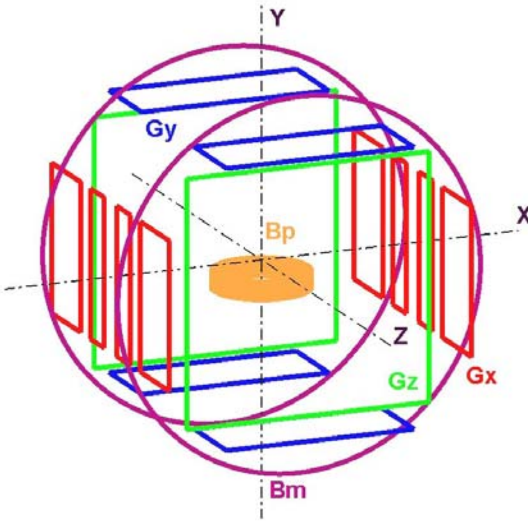
I. M. Savukov, S. J. Seltzer, M. V. Romalis and K. L. Sauer. "[Tunable Atomic Magnetometer for Detection of Radio-Frequency Magnetic Fields.]" *Phys. Rev. Lett.* **95**, 063004 (2005).

I. M. Savukov, S. J. Seltzer, and M. V. Romalis. "[Detection of NMR signals with a radio-frequency atomic magnetometer.]" *Journal of Magnetic Resonance.* **185**, 214 (2007).

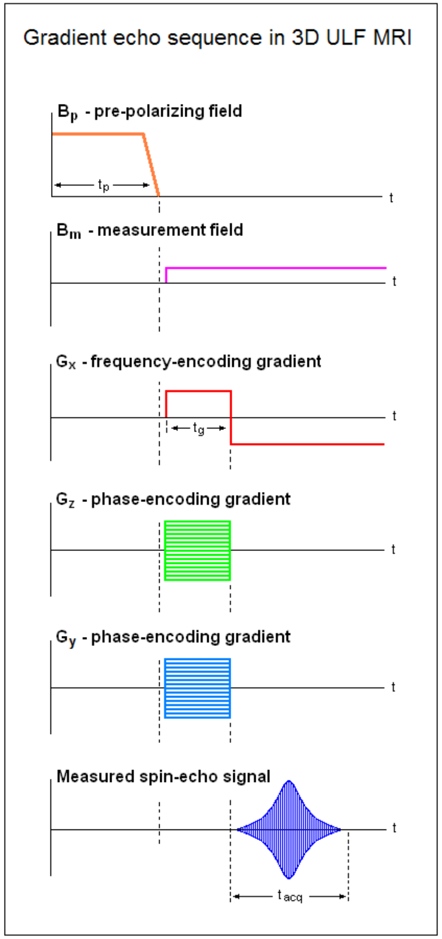
Next step – MRI with AM

General view of the system

Schematic of the coil system



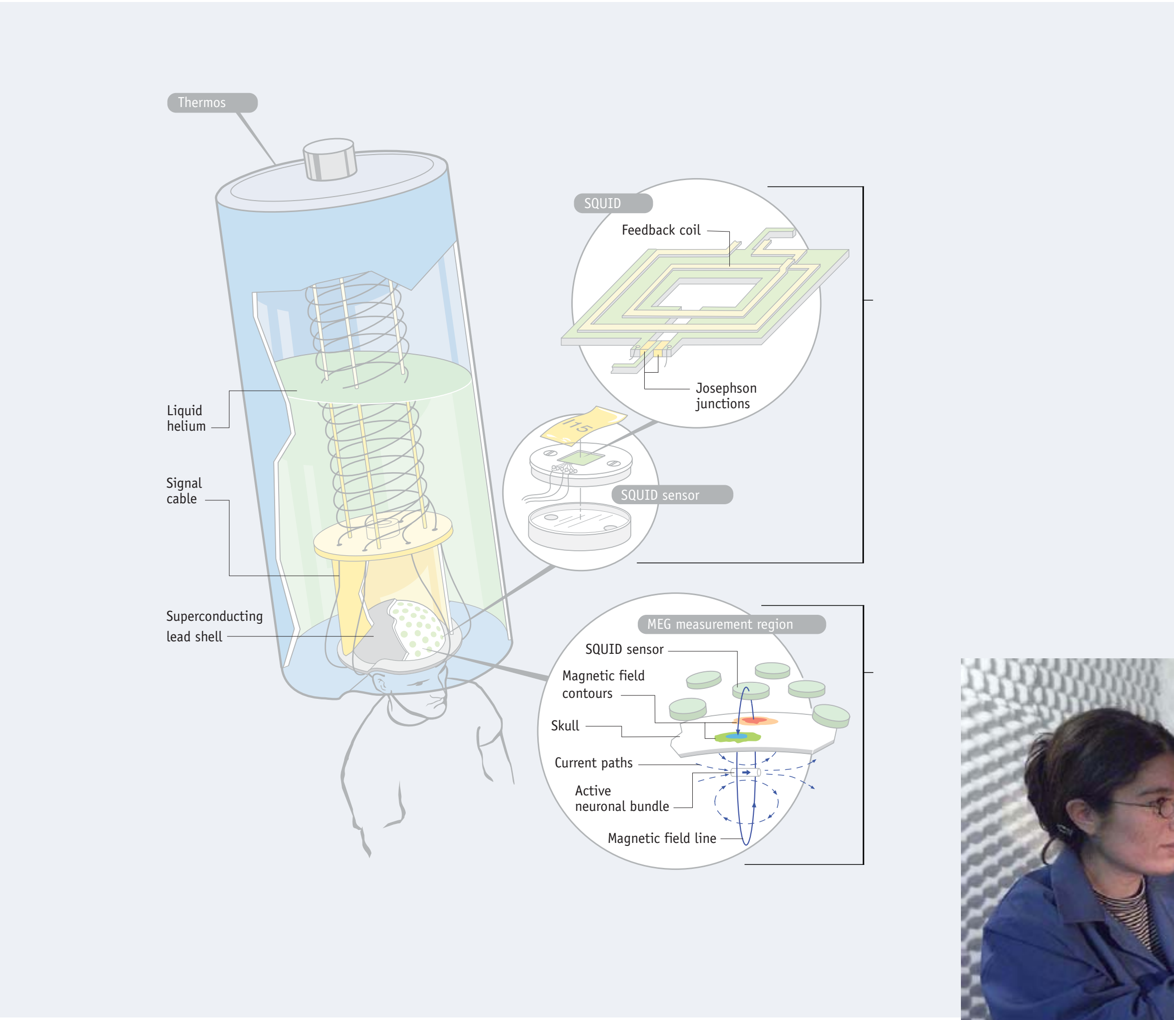
Imaging protocol



Replace SQUID with AM

Los Alamos Laboratory, SQUID team ULF MRI setup

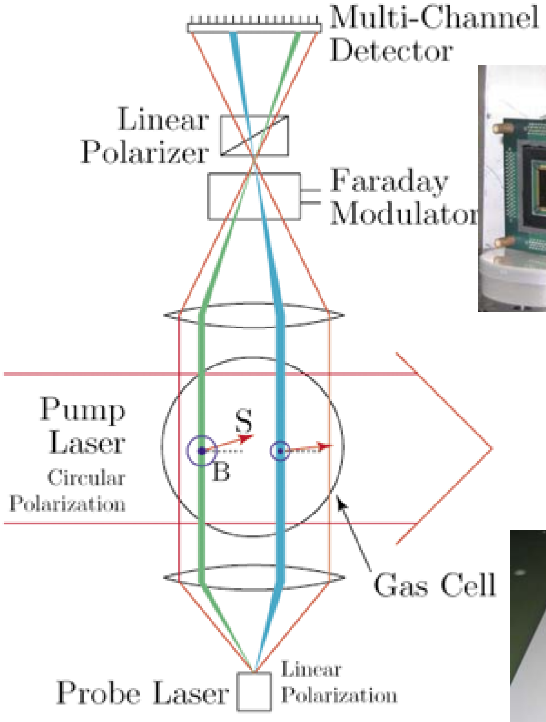
MEG with SQUIDs

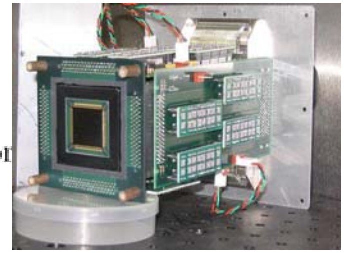


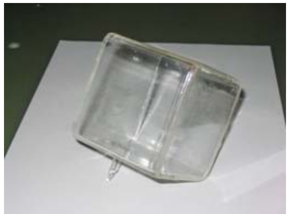
Los Alamos Laboratory,
SQUID team

MEG with SERF magnetometer

Princeton MEG system
based on SERF magnetometer

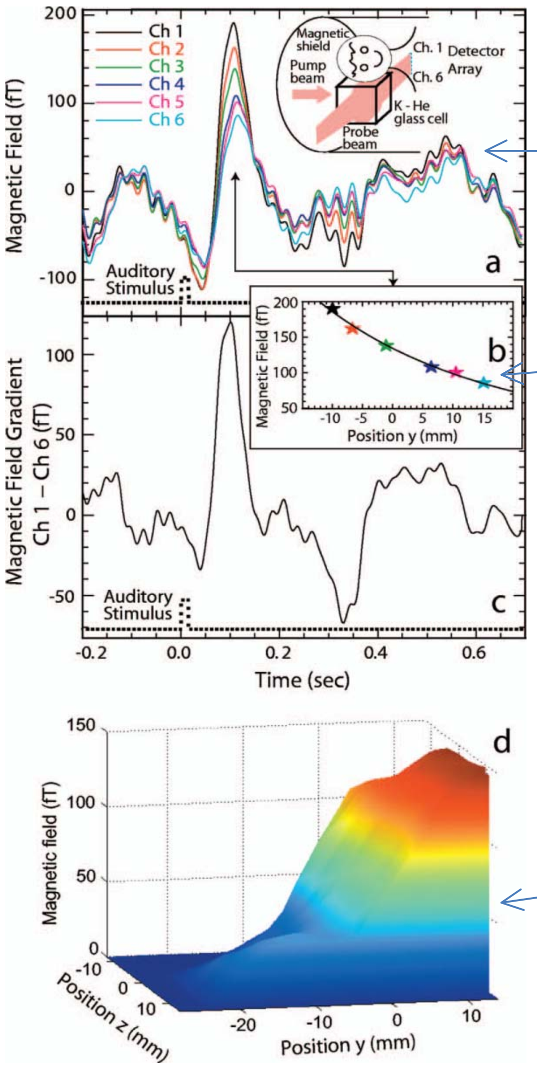






H. Xia, A. Ben-Amar Baranga, D. Hoffman, and M. V. Romalis. "Magnetoencephalography with an atomic magnetometer." *Appl. Phys. Lett.* **89**, 211104 (2006)

First MEG detection with AM



6 channel field recordings

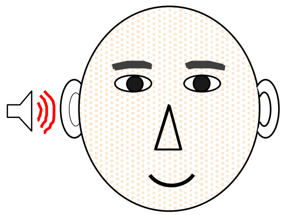
Localization of a MEG source

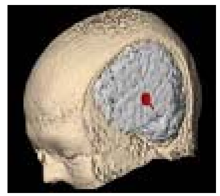
Magnetic field topography

H. Xia, A. Ben-Amar Baranga, D. Hoffman, and M. V. Romalis, Appl. Phys. Lett. 89, 211104 (2006)

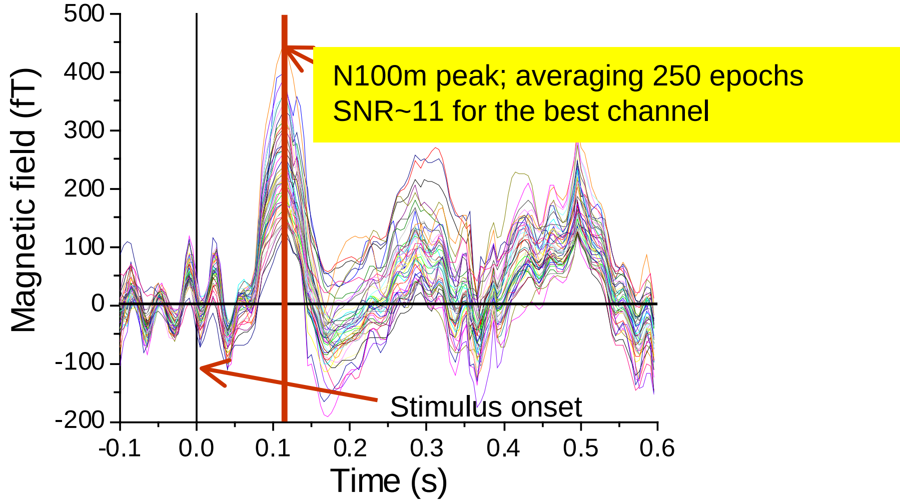
Auditory Evoked Field (AEF) Measurement

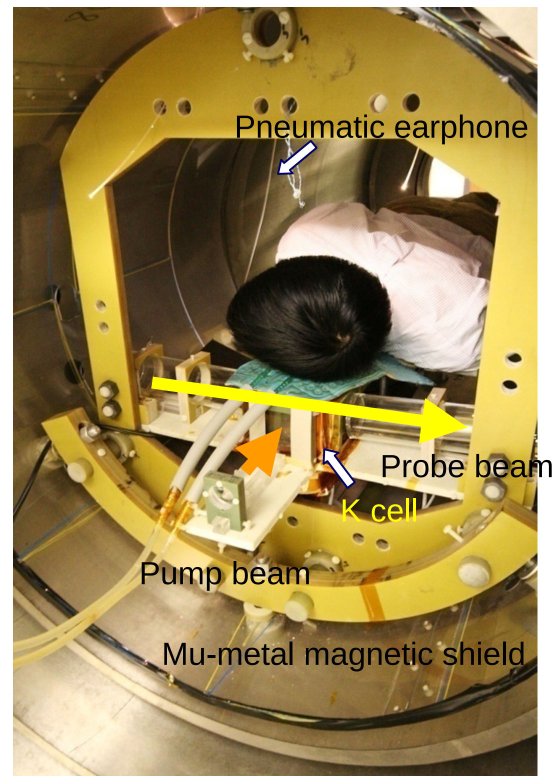
Auditory stimulus
on **Right** ear :
500 kHz tone,
100 ms duration



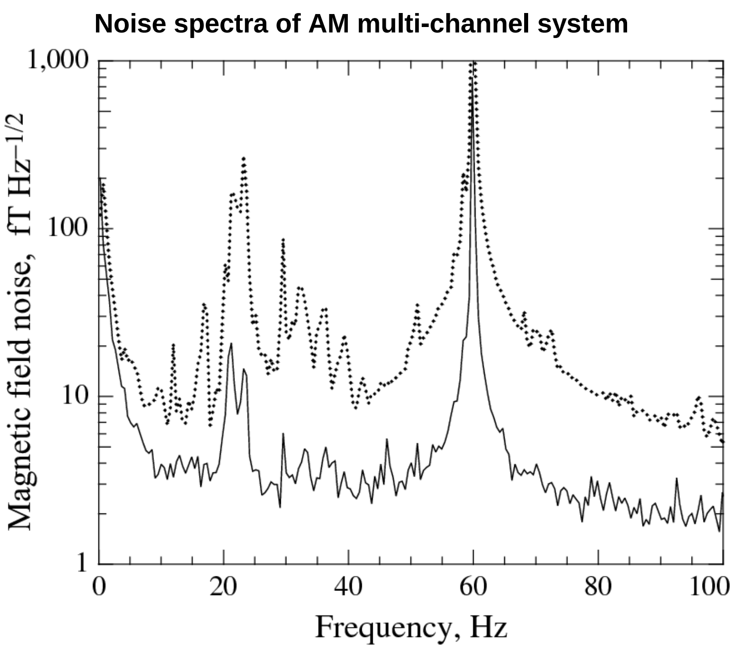


Primary auditory cortex
excitation after 100 ms

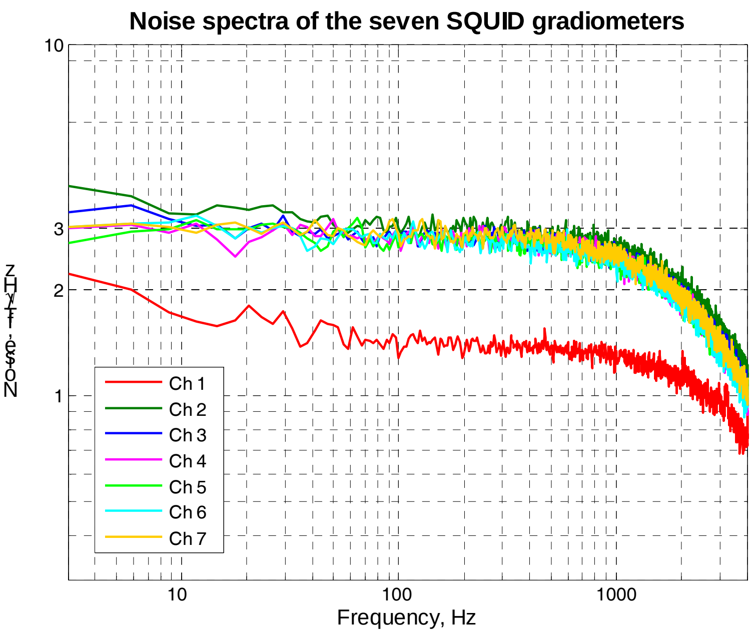




Noise performance



Princeton, Romalis group



Los Alamos, SQUID team

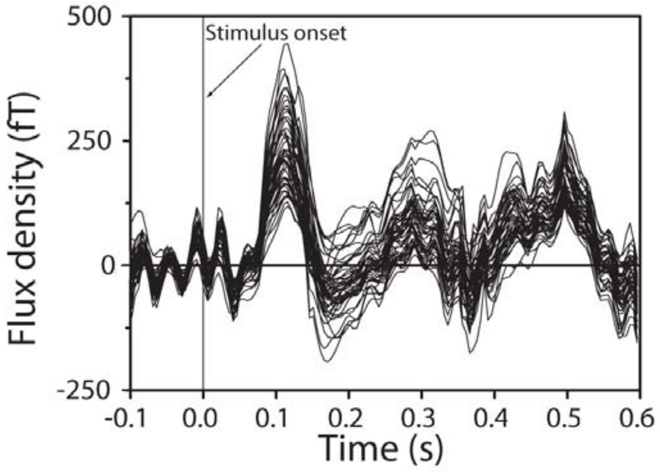
Single Channel noise: 10 fT/Hz$^{1/2}$

With noise cancellation between channels: 3.5fT/Hz$^{1/2}$

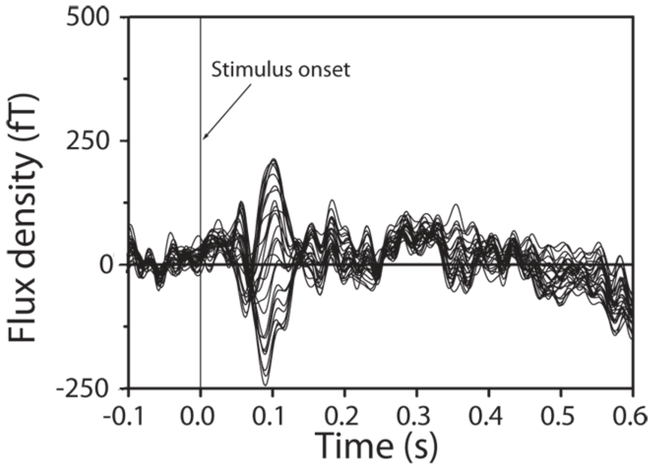
Bandwidth ~ 40 Hz

Atomic Brain Signal vs. SQUID Brain Signal

Atomic magnetometer

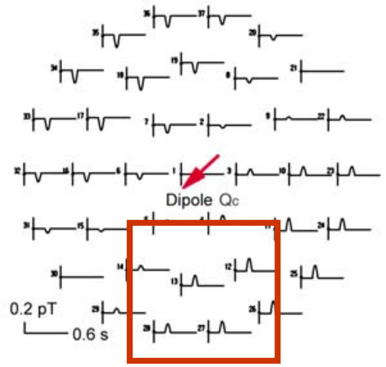


SQUID helmet



Single magnetic field polarity in the result of the atomic brain magnetometer

→ originated from the fact that the measurement area is not enough to cover the dipolar magnetic field pattern



Conclusions

- AM is emerging new technology, competing with SQUIDs in biomedical applications
- MEG is demonstrated with AM
- NMR is demonstrated with AM
- Future: applications to MRI
- DNI – direct neural imaging

Traumatic Brain Injury in OIF/OEF – A Case Report

Deborah L. Warden, MD
David Moore, MD, PhD
Leslie Shupenko, MS, Louis French, PsyD
Gerard Riedy, MD, PhD
Defense and Veterans Brain Injury Center
Washington, DC

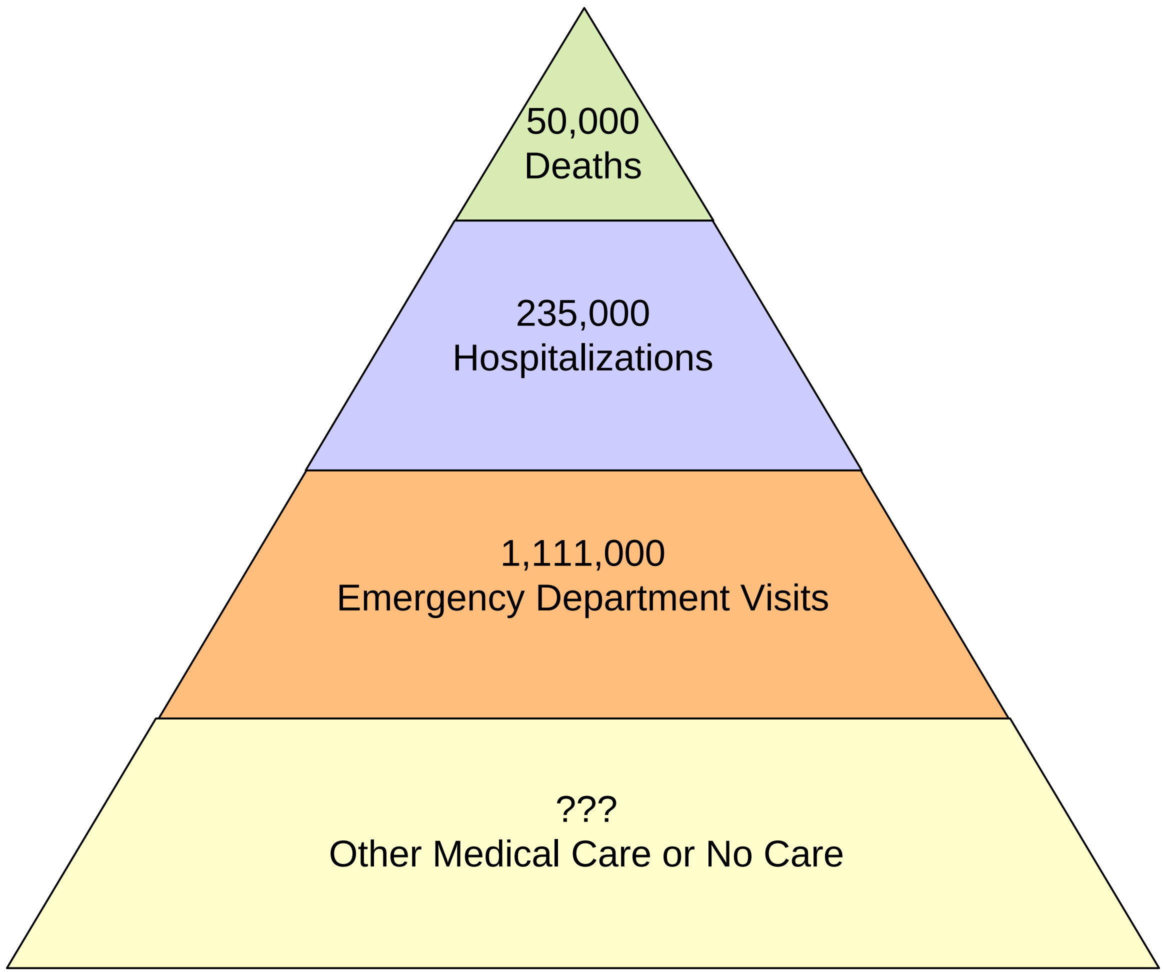
Disclaimer

The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army, Department of Defense, or the U.S. Government.

Talk Overview

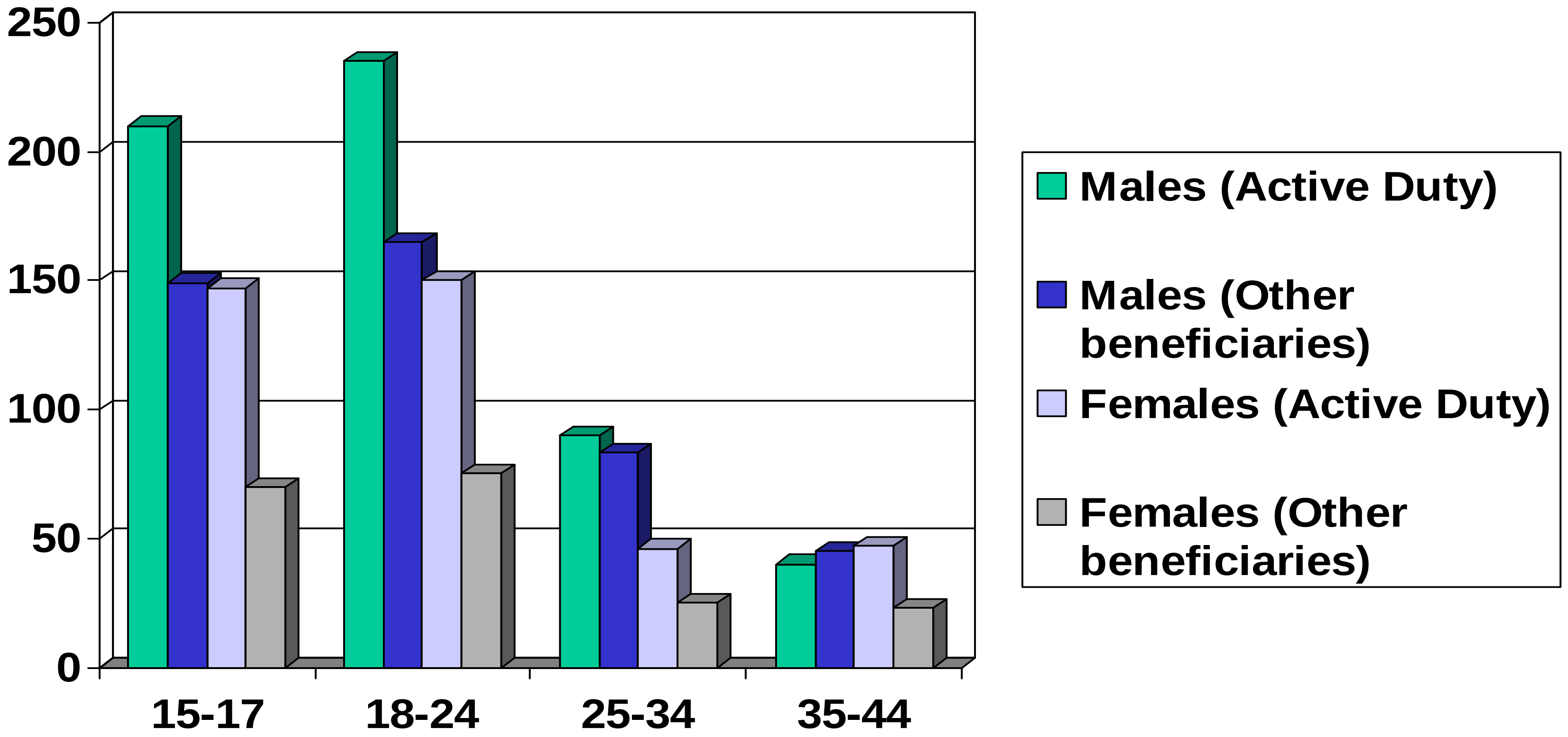
- Military/ civilian epidemiology
- Relevance of TBI to military
- Blast Injury
- Data from Defense and Veterans Brain Injury Center

Relative Proportion of Levels of Care for TBI



Source: CDC: Traumatic Brain Injury in the United States, October 2004

Head Injury in the U.S. Military



Ommaya AK, Ommaya AK, Dannenberg AL, Salazar AM. Causation, incidence, and costs of traumatic brain injury in the U.S. Military Medical System. *J Trauma*. 1996

Missed TBI Diagnoses*

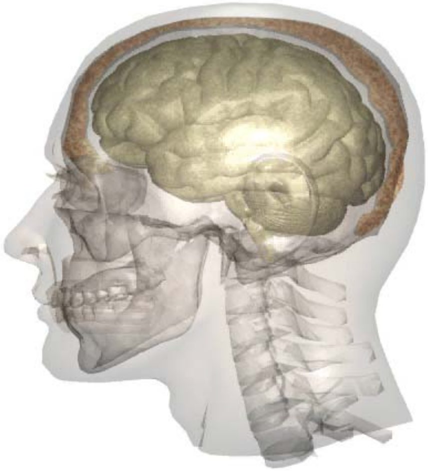
51% of 47 patients seen in a British trauma center with a TBI did not have a TBI diagnosis recorded

Most TBI patients lacking a coded TBI diagnosis had other injuries coded

*TBI defined as any injury to the head and some gap in memory for events.

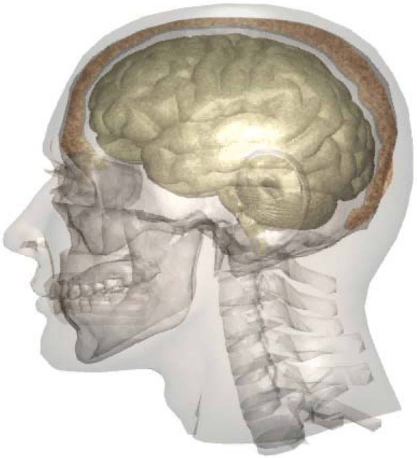
Moss NEG, Wade DT. Admission after head injury: How many occur and how many are recorded?. *Injury*. 1996; 27(3): 159-161.

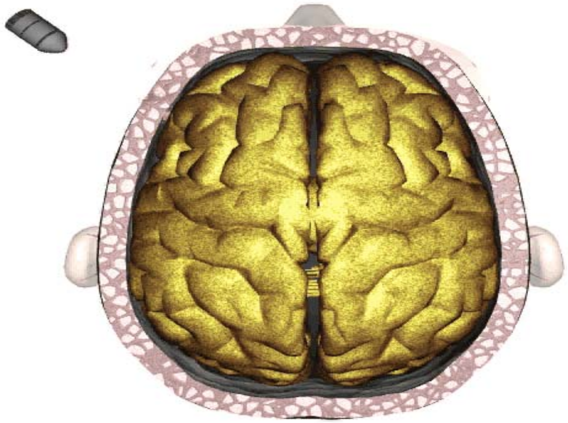
Mechanisms of Injury



Diffuse Axonal

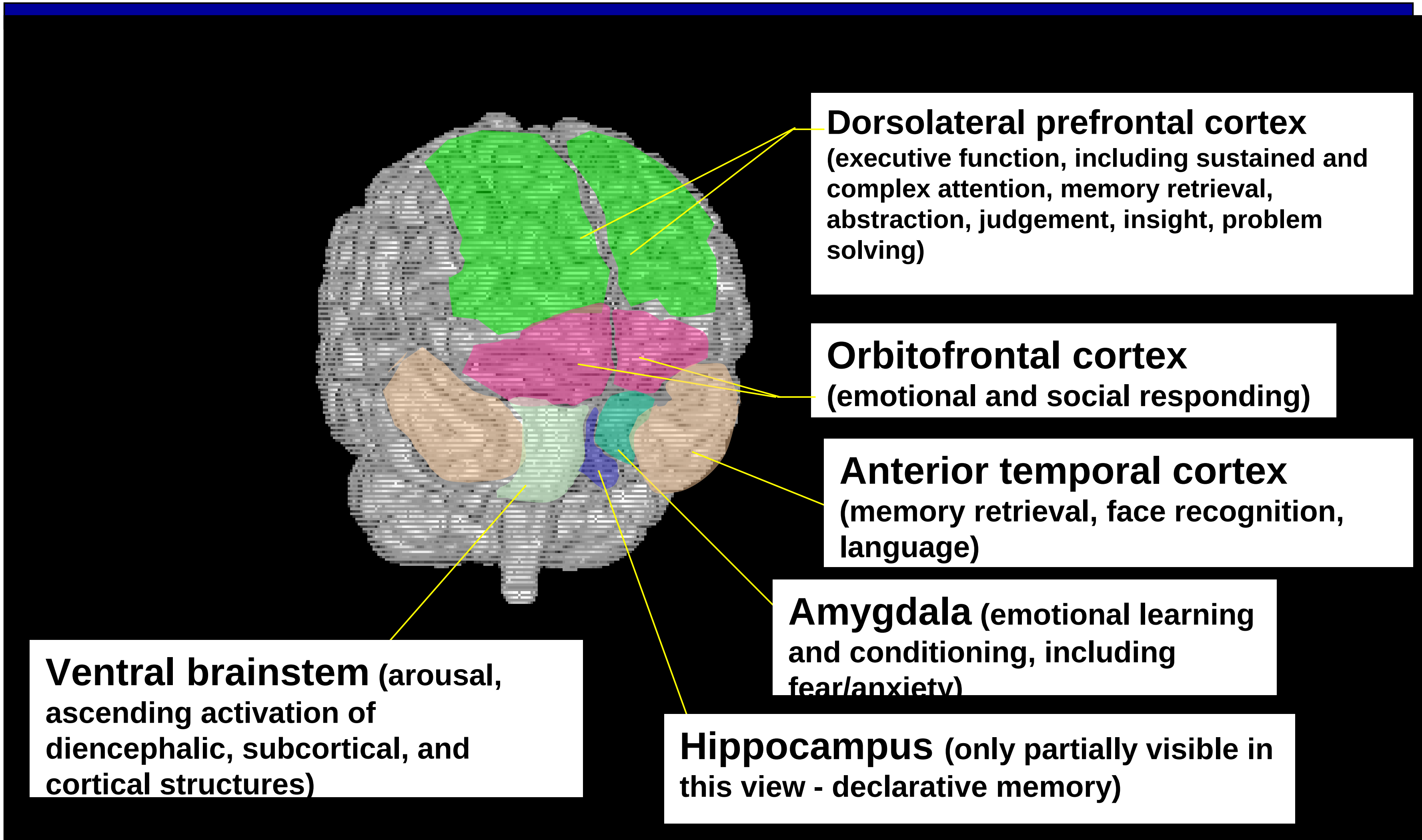
Contra coup





Penetrating
Gun Shot
Wound

Regional Cortical Vulnerability to TBI Predicts Neuropsychiatric Sequelae



Postconcussion Symptoms (PCS)

- Headache
- Dizziness
- Irritability
- Decreased Concentration
- Memory Problems
- Fatigue
- Visual Disturbances
- Sensitivity to Noise
- Judgement Problems
- Anxiety
- Depression

Neurocognitive Changes

Attention/Concentration

Speed of Mental Processing

Learning/Information Retrieval

Executive Functions (e. g., Planning, Problem Solving, Self Monitoring) May see judgment problems, apathy, inappropriate behaviors

Post Concussive Sx in Mild TBI

- Natural history is recovery within weeks/months (Levin 1987), but a small percentage will have persistent symptoms (Alexander, Neurology 1995)
- High school athletes with 3 or more prior concussions were up to 9 times more likely to develop symptoms than athletes without prior injury (Collins, et al, Neurosurgery 2002)
- Educational interventions effective in reducing symptoms (Ponsford, et al. 2002)

TBI Incidence - WRAMC

Battle and NonBattle Injuries

- 429/2294 with TBI
- 19% with TBI

Battle Injuries Only

- 342/1116 with TBI
- 31% with TBI

Blast Injuries

Multifactorial injury mechanism:

1. **Primary**: Direct exposure to overpressurization wave – velocity >/= 300m/sec (speed of sound in air)
2. **Secondary**: Impact from blast energized debris – penetrating and nonpenetrating
3. **Tertiary**: Displacement of the person by the blast and impact G. Cooper, et al 1983

4. **Quaternary**: Burns/Inhalation of gases

- May be combined with MVA in war theater

Blast Injuries

- Primary blast injury: interaction of the overpressurization wave and the body. Air-filled organs vulnerable: ear, lung, and GI tract
- The brain is also vulnerable: direct injury, e.g. cerebral contusion; indirect injury, e.g. cerebral infarction secondary to air emboli (Elsayed, 1997;Mayorga, 1997). Data on non-fatal blast closed brain injury are limited.
- Lab studies have found that blast, even while the head was protected, causes structural changes in the brain and cognitive impairments. There is also a significant linear relationship between blast injury severity and task impairment (Cernak I, et al. 2001).

Primary Blast Injury: A Case Report of SGT B

- 50 y/o SGT in Iraq walking back to quarters
- Explosion hit the ammo area of their own base
- Sgt B – crouched behind a 5 inch thick cement bunker with vest and helmet
- exposure to 3 hours of explosions – 10/2006
- 3 episodes of “having her bell rung” concurrent with “chest hurt” – once when she peered outside as a new explosion occurred
- Did not fall or hit her head at any point

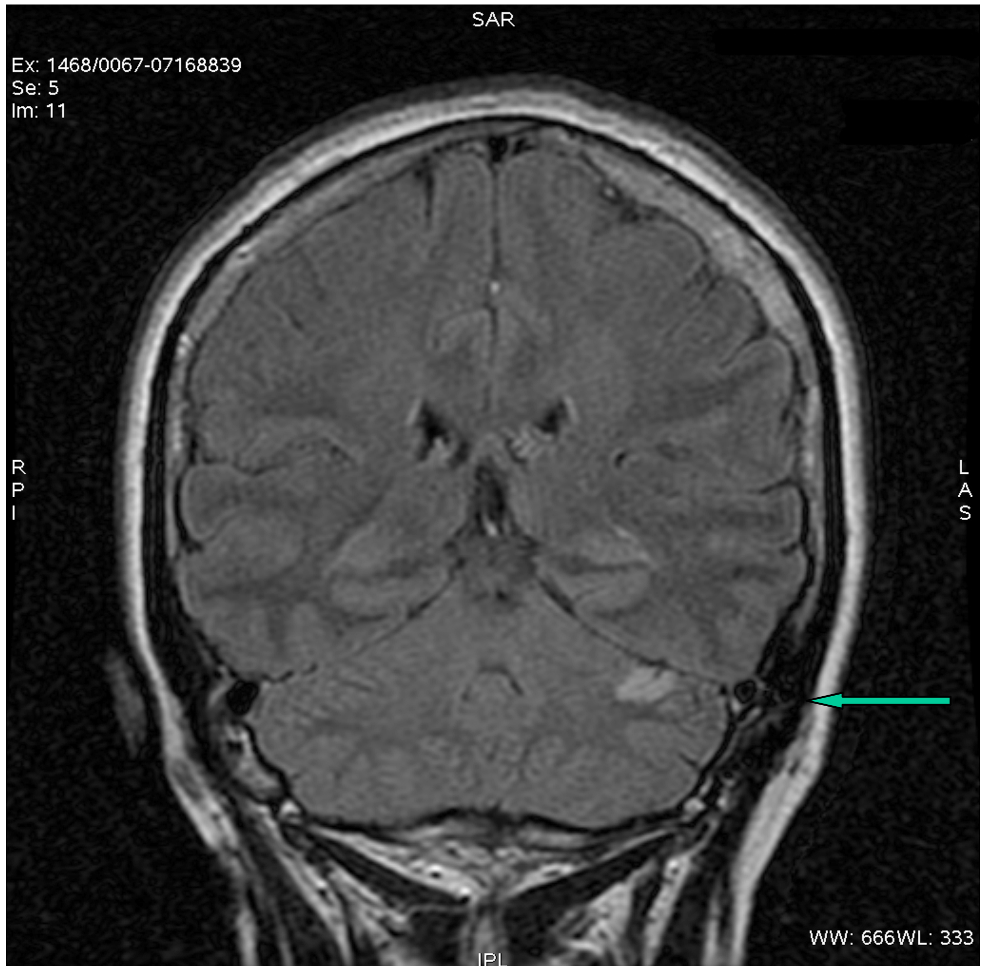
Primary Blast Injury: A Case Report of SGT B

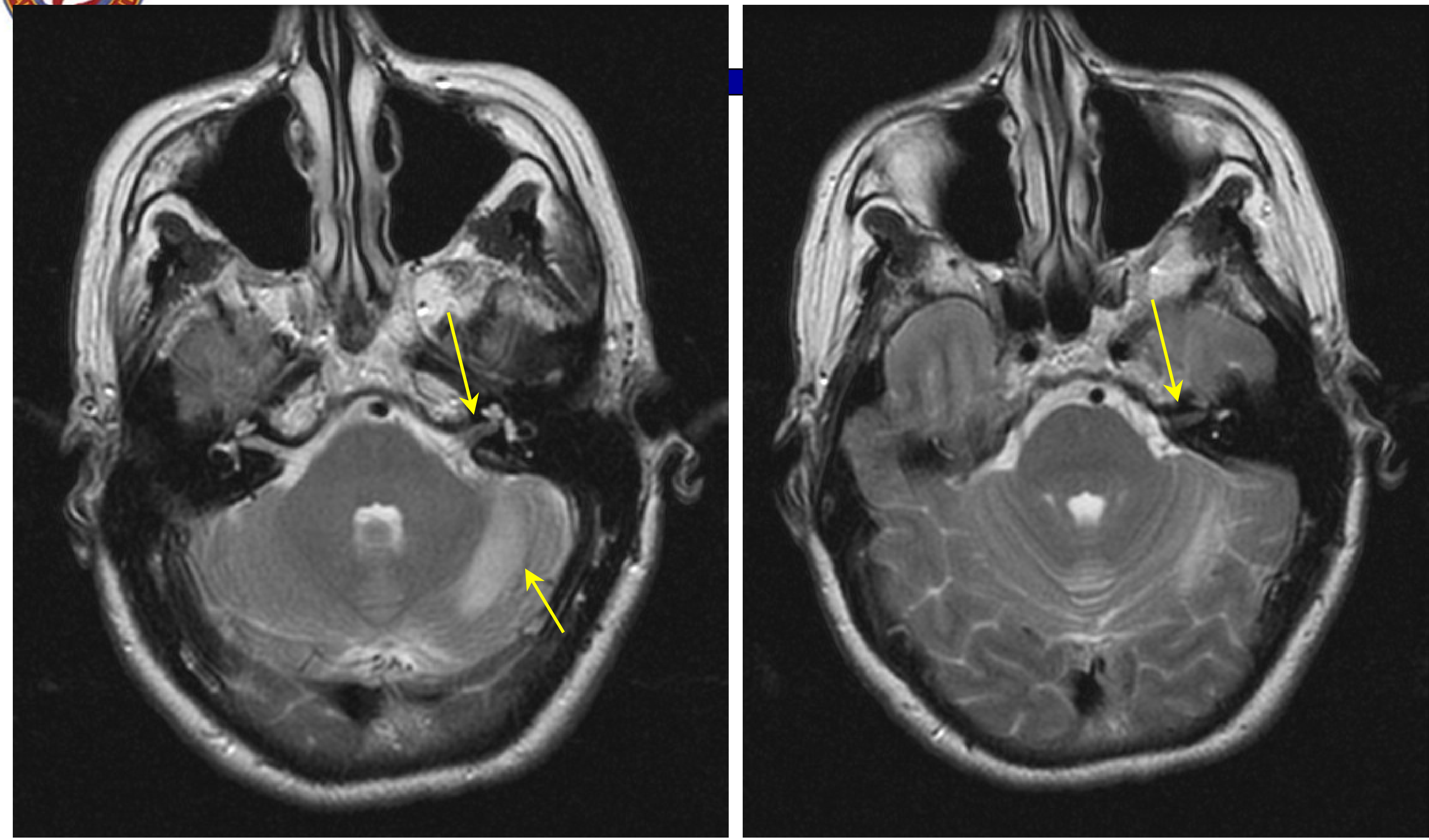
- Immediate aftermath –
  - 2 weeks of headache, dizziness, balance problems, nausea/vomiting – treated initially for dehydration d/t vomiting; also insomnia, anxiety, nightmares
  - Gradually felt better, remained at admin position in Iraq; felt more subdued, not her usual extroverted self
- Past Medical History –
  - 9/06 inside vehicle that encountered an explosion -
    - "a little jolting"; tinnitus; ear exam – irritation in Left ear
    - Did not hit her head

Primary Blast Injury: A Case Report of SGT B

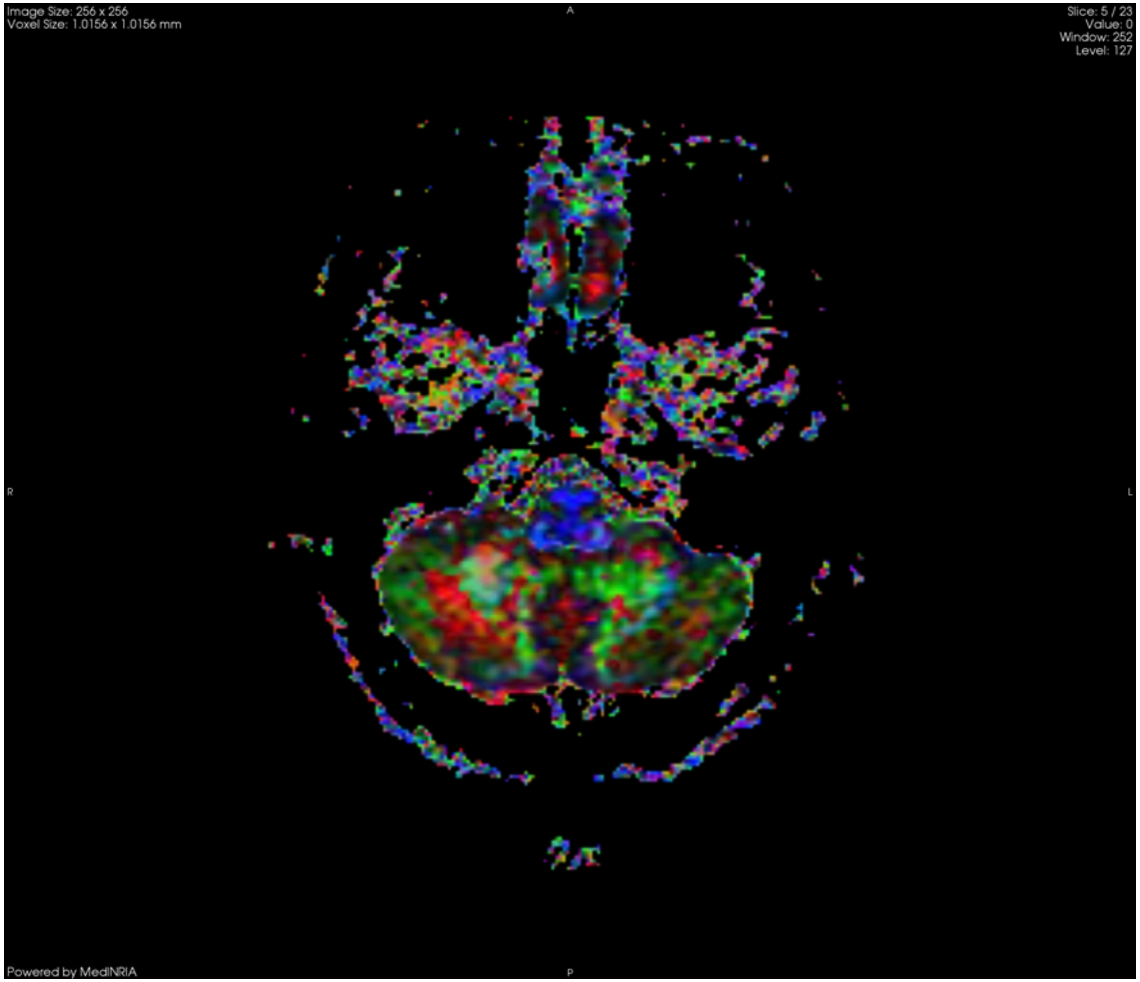
- Habits – never smoked; rare etoh
- Former medic, break in service to raise family
- MR imaging – see slide
- F/u MRI 3 months later – see slide

FLAIR March 2007

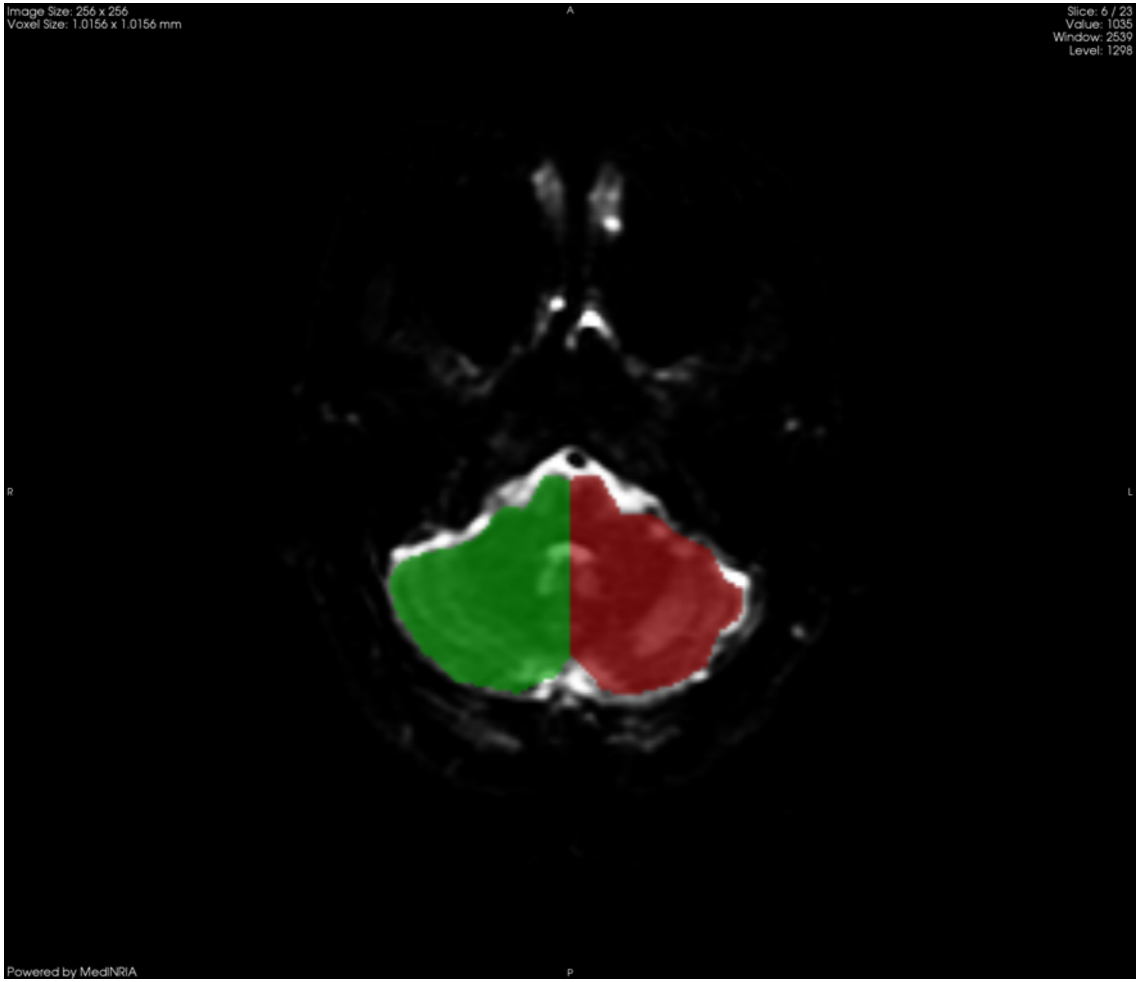




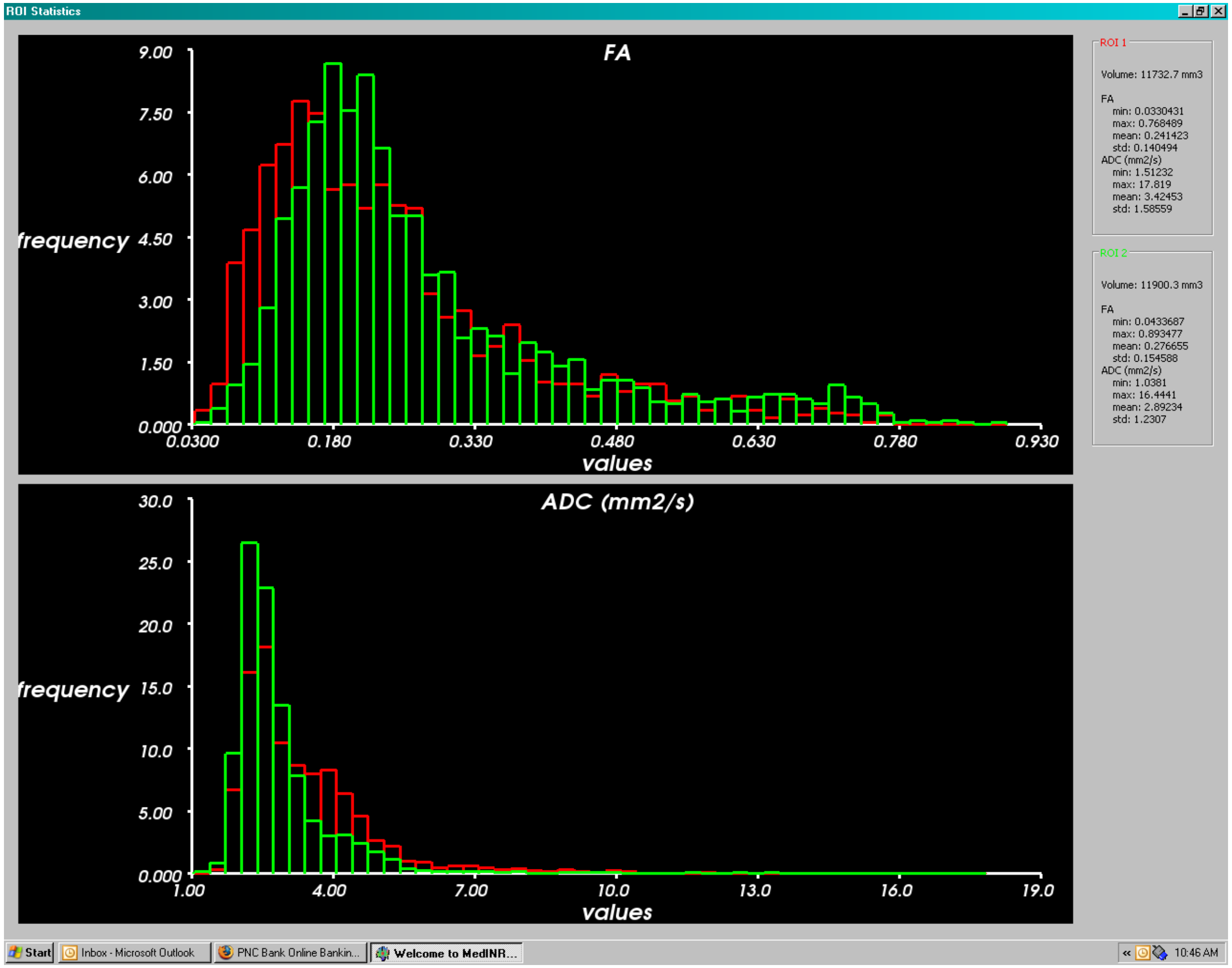
Color Coded Orientation Map



Hemi-Cerebellar ROI
March 2007

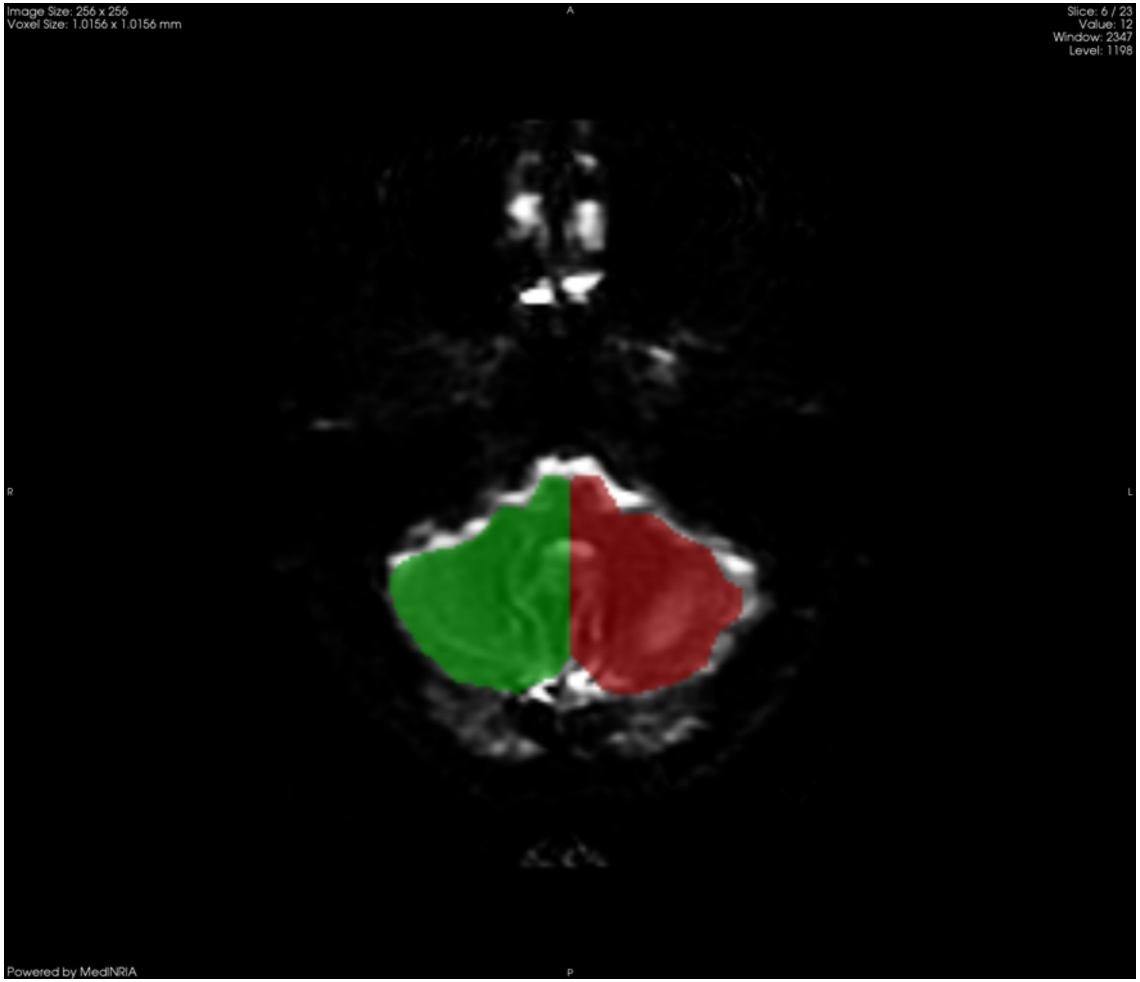


Histogram March 2007

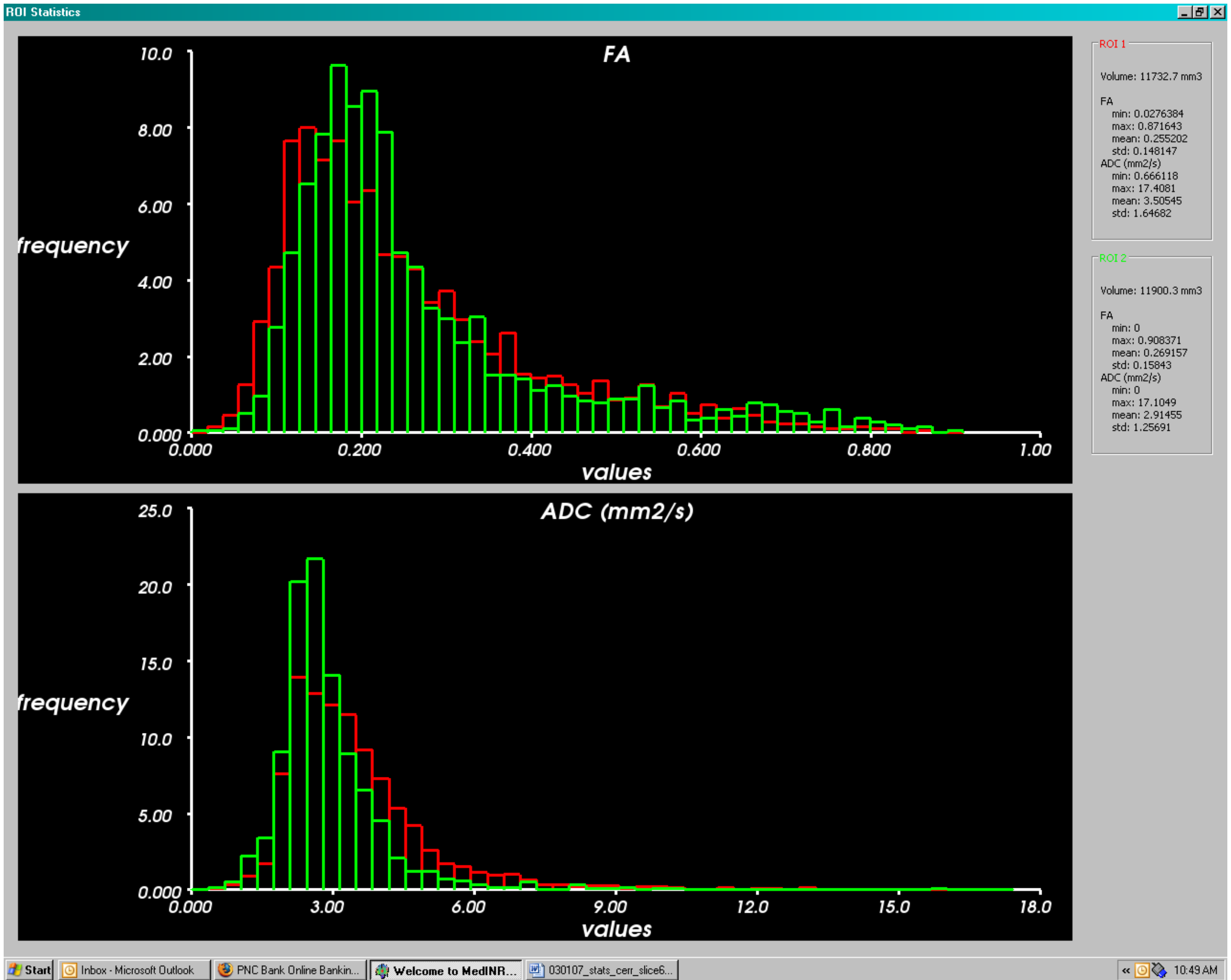


Tractography March 07

Hemi-Cerebellar ROI May 2007



Histogram May 2007



Primary Blast Injury: A Case Report of SGT B

- Conclusion –
  - Rare instance of clear exposure to primary blast without secondary or tertiary blast
  - Clear post concussive symptoms – H/A, balance problems, dizziness, nausea/vomiting x 2 weeks
  - MR findings consistent with brain injury dated to October 2006
  - Resilience is apparent as this soldier continues on Active Duty and is resuming full career with the Army

Defense and Veterans Brain Injury Center (DVBIC)

Toll Free Referral and Information Line:

1-800-870-9244

Web Site: www.DVBIC.org

Detection of White-Matter Pathways affected in TBI by DTI-Tractography

Manbir Singh
Radiology and Biomedical Engineering
University of Southern California
Los Angeles, CA, USA

Introduction

- Sudden Acceleration/Deceleration or Rotational/Vibrational forces induce Diffuse Axonal Injury (DAI).
- DAI causes wide range of neurological problems including cognitive impairments.
- Routine CT/MRI under-diagnose DAI.
- DAI disrupts axonal membranes and cyto-skeletal network.
- DTI ideal for detection of membrane dis-ruption, DTI-tractography ideal for detection of network and pathway disruptions.

Diffusion Weighted MRI

- Random motion of water molecules in biological tissues is restricted by microstructures
- MRI signal is sensitive to displacement along the direction of gradients.

Diffusion Tensor (Basser 1994)

$$A = \exp\left(-bD\right)$$

A : Attenuation of the MRI signal

b : "b factor" characterizing the gradient pulses(timing, amplitude, shape) (s/mm^2)

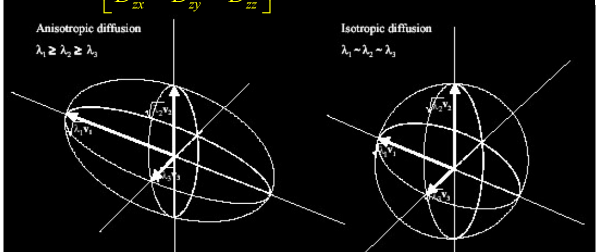
D : Diffusion Tensor (mm^2/s)

$$D = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix}$$

Principal Components

$$D = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix} \Rightarrow$$

Eigenvectors
Eigenvalues

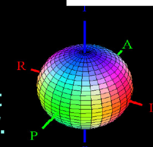


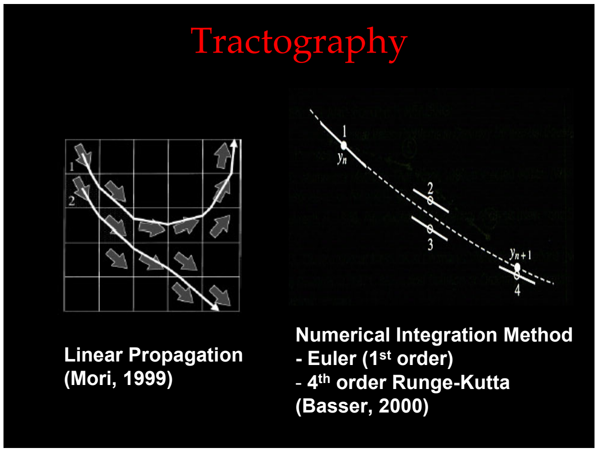
Fractional Anisotropy (FA)

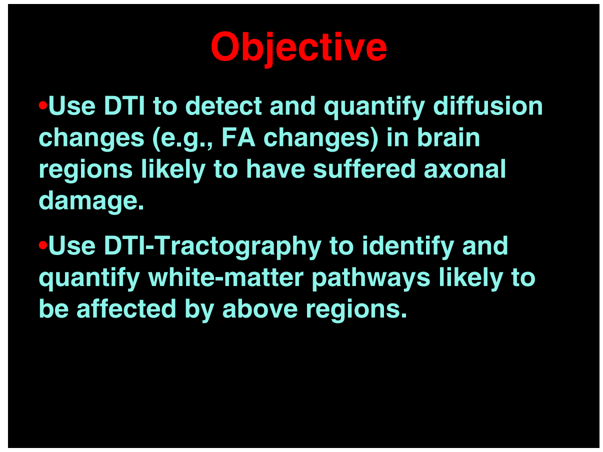
- Degree of anisotropy calculated by Fractional Anisotropy

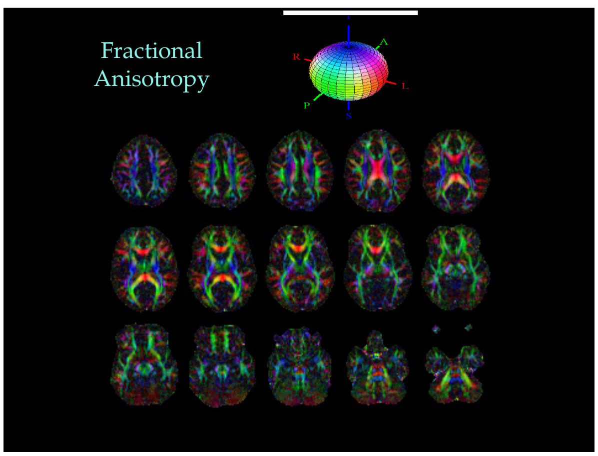
$$FA = \frac{\sqrt{3\left[\left(\lambda_1-\langle\lambda\rangle\right)^2+\left(\lambda_2-\langle\lambda\rangle\right)^2+\left(\lambda_3-\langle\lambda\rangle\right)^2\right]}}{\sqrt{2\left(\lambda_1^2+\lambda_2^2+\lambda_3^2\right)}}$$

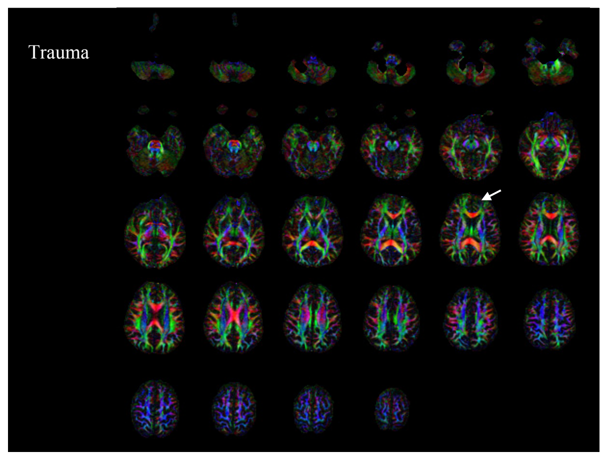
- Eigenvector with the largest eigenvalue assumed to represent the fiber orientation (Pajevic *et al.* 1999)

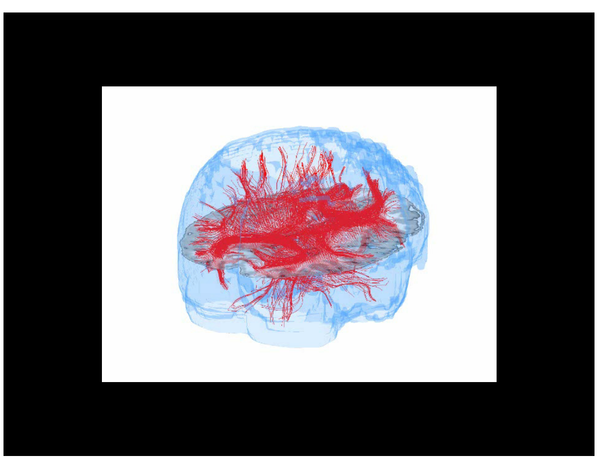


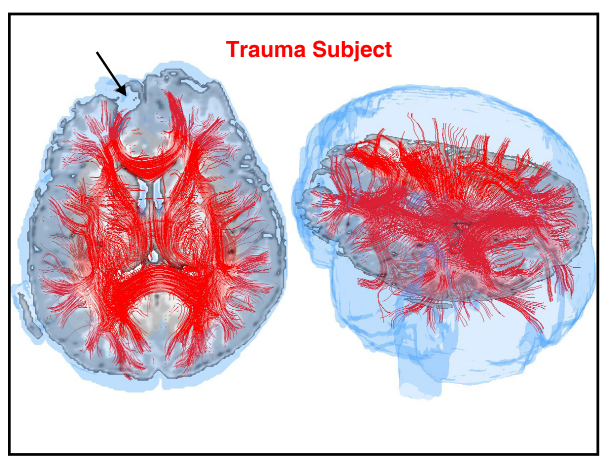

Tractography
Linear Propagation
(Mori, 1999)
Numerical Integration Method
- Euler (1st order)
- 4th order Runge-Kutta
(Basser, 2000)


Objective
•Use DTI to detect and quantify diffusion changes (e.g., FA changes) in brain regions likely to have suffered axonal damage.
•Use DTI-Tractography to identify and quantify white-matter pathways likely to be affected by above regions.


Fractional
Anisotropy


Trauma



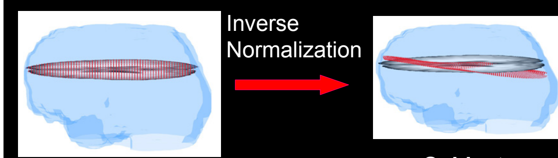

Trauma Subject

FA differences (Normalized)

- Construct FA map for each TBI patient and 10 age-matched Normal control subjects.
- Normalize all FA maps to a standard space (we use SPM space) using non-linear normalization and a FA template constructed from our 10 normal subjects.
- Construct voxel based T-map of FA differences between TBI patient and 10 normals. Set threshold to identify ROIs.

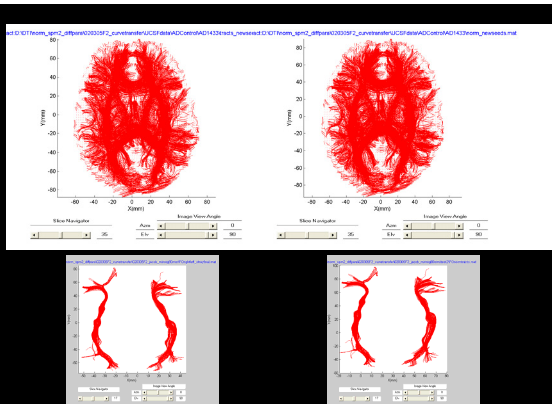
Tractography Normalization Procedure

Use same number of seeds in each subject at anatomically equivalent locations



Template **Subject**

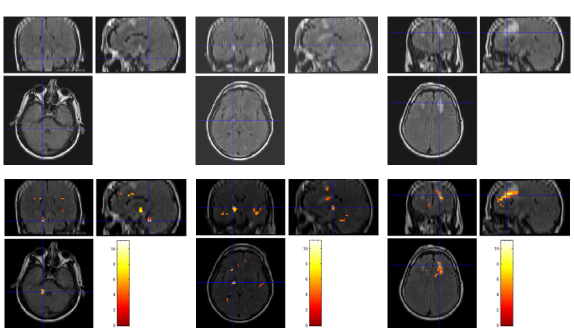
We used an FA template in SPM standard space for normalization



Subject Space **Normalized Space**

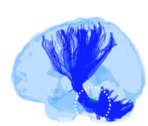
RESULTS

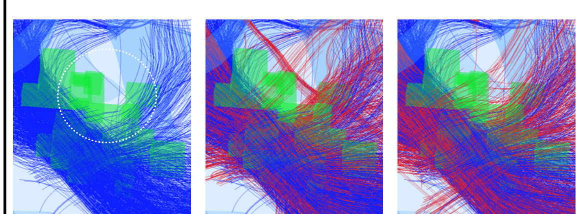
Trauma subject #1



Trauma case 1: ROI #1

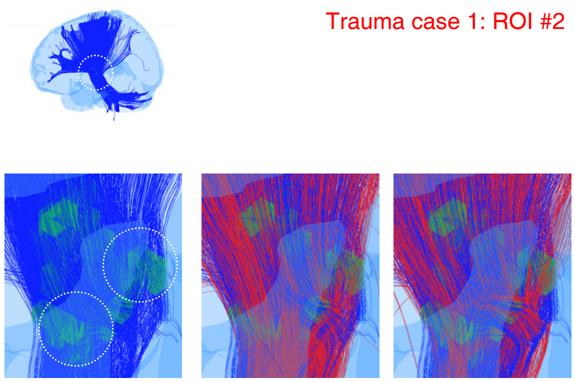
Normalized Space Tractography





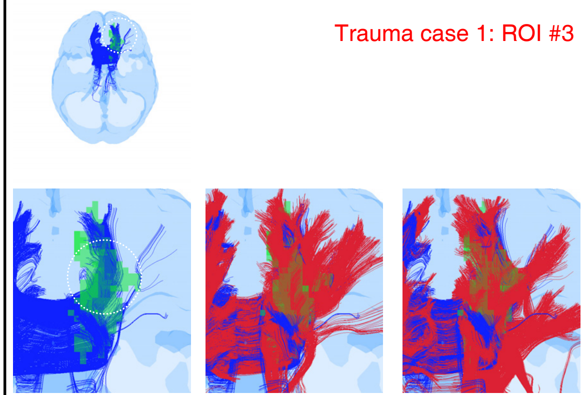
Trauma subject Trauma vs. Normal #1 Trauma vs. Normal #2

Trauma case 1: ROI #2



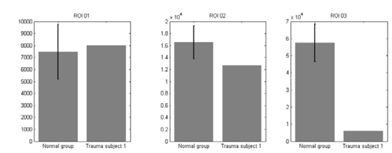
Black dotted: Broken fibers   Trauma vs. Normal #1   Trauma vs. Normal #2

Trauma case 1: ROI #3



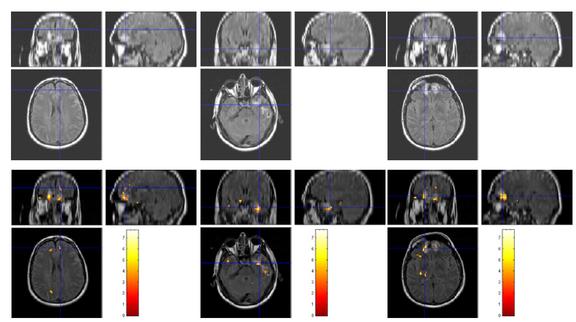
Black dotted: Broken fibers   Trauma vs. Normal #1   Trauma vs. Normal #2

Tract Counts in ROIs

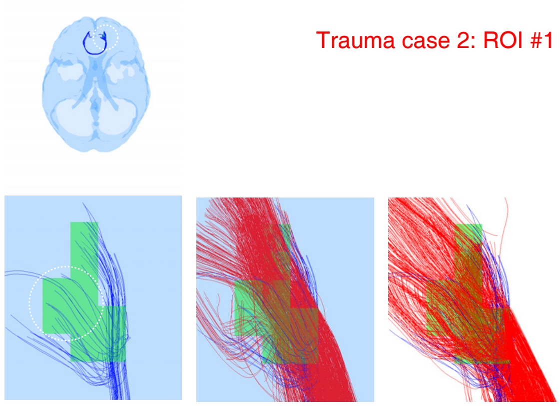


		ROI 1	ROI 2	ROI 3
Normal group	Mean	7461	16508	57498
	STD	2285	2756	10919
Trauma subject 1		8006	2646	6006

Trauma case 2

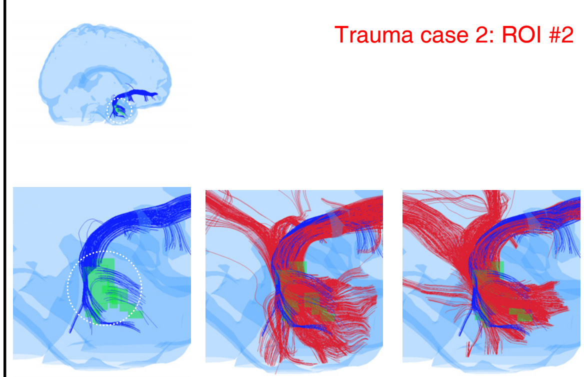


Trauma case 2: ROI #1



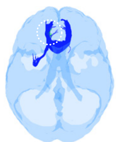
Black dotted: Broken fibers   Trauma vs. Normal #1   Trauma vs. Normal #2

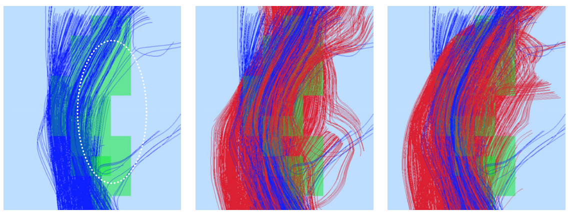
Trauma case 2: ROI #2



Black dotted: Broken fibers   Trauma vs. Normal #1   Trauma vs. Normal #2

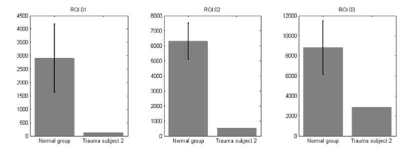
Trauma case 2: ROI #3





Black dotted: Broken fibers | Trauma vs. Normal #1 | Trauma vs. Normal #2

Tract counts in ROIs



		ROI 1	ROI 2	ROI 3
Normal group	Mean	2912	6304	8800
	STD	1277	1182	2695
Trauma subject 2		136	537	2870

Summary

- DTI is well-suited to detect DAI in TBI
- Preliminary results suggest that FA and tractography differences can be quantified to detect injured regions and the pathways affected by these injured regions

Ethical Issues in Neuro-Imaging

Gregory P. Lekovic, MD, PhD, JD
Chief Resident, Neurological Surgery
Barrow Neurological Institute
Phoenix, AZ
Adjunct Professor of Law
Sandra Day O'Connor School of Law
Arizona State University
Tempe, AZ

Overview of Ethical Concerns with Neuro-Imaging: fMRI, PET, SPECT, MEG

1. Premature adoption of technology/ Misapplication
    1. Reliability/ validity of results
        1. Different standard for science, law, business
2. Privacy and ‘collateral information’
    1. Are all brain imaging tests fundamentally ‘medical’ in nature?
        1. HIPPA, duty to disclose?
    2. Is there an inherent privacy interest in cognitive data?
3. Forensic or Legal use
    1. How will courts interpret neuro-imaging data?

Wople, et al AJOB 5(2): 39-49 (2005)

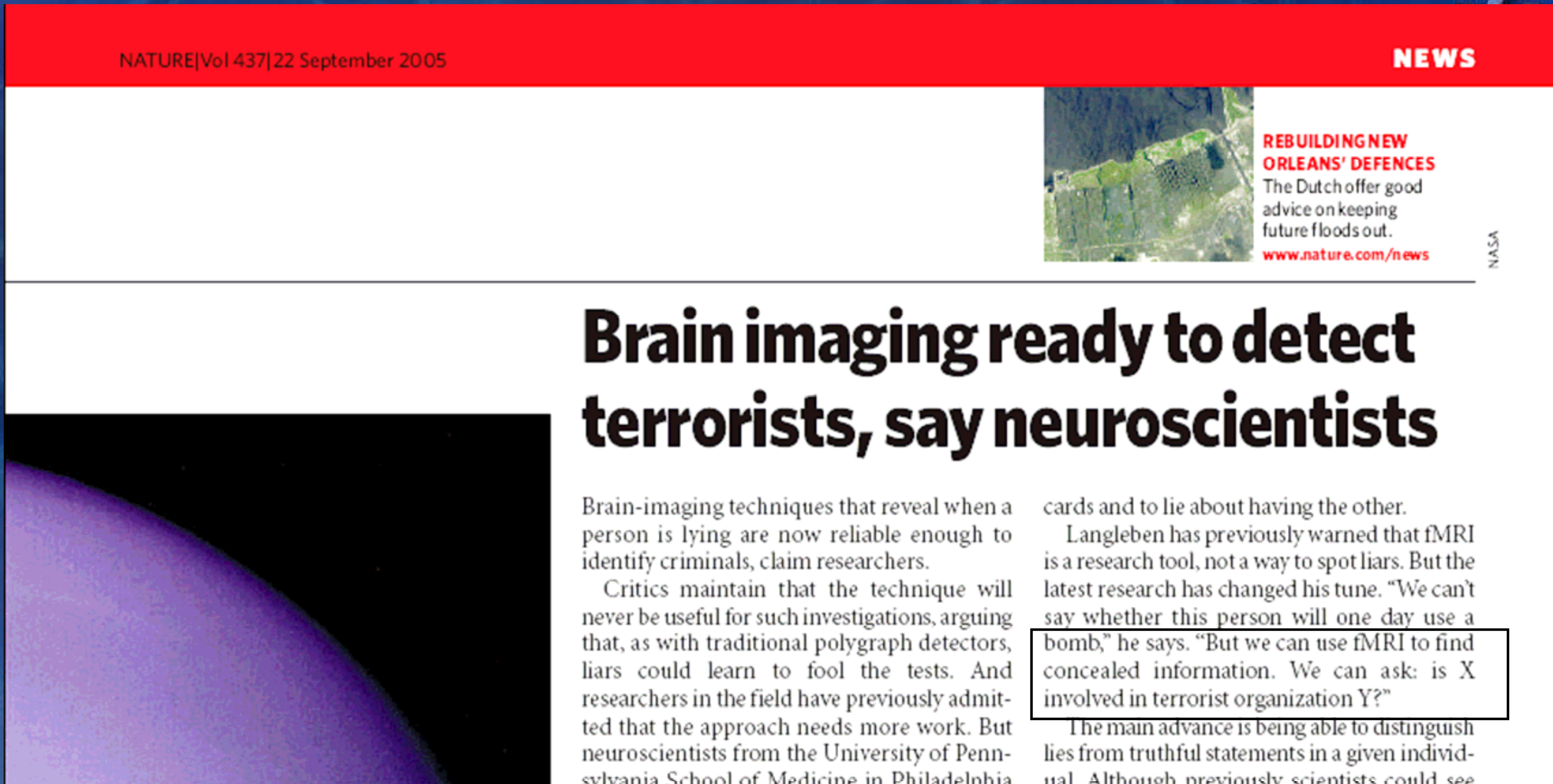
Examples

1. Image based diagnoses- PTSD, etc
   - Validity
   - Privacy/ Collateral information
   - Forensic (mis)use
2. Image guided therapies, e.g. surgery for psychiatric disease
   - Validity/ misapplication
   - Privacy & collateral information- not an issue if seeking treatment
   - Forensic (mis)use

Overview of Ethical Concerns with Neuro-Imaging

1. ***Premature adoption of technology/ Misapplication***
2. Privacy/ Collateral information
3. Forensic use

Wople, et al AJOB 5(2): 39-49 (2005)



NATURE|Vol 437|22 September 2005 NEWS

REBUILDING NEW ORLEANS' DEFENCES
The Dutch offer good advice on keeping future floods out.
www.nature.com/news

NASA

Brain imaging ready to detect terrorists, say neuroscientists

Brain-imaging techniques that reveal when a person is lying are now reliable enough to identify criminals, claim researchers.

Critics maintain that the technique will never be useful for such investigations, arguing that, as with traditional polygraph detectors, liars could learn to fool the tests. And researchers in the field have previously admitted that the approach needs more work. But neuroscientists from the University of Pennsylvania School of Medicine in Philadelphia

cards and to lie about having the other.

Langleben has previously warned that fMRI is a research tool, not a way to spot liars. But the latest research has changed his tune. "We can't say whether this person will one day use a bomb," he says. "But we can use fMRI to find concealed information. We can ask: is X involved in terrorist organization Y?"

The main advance is being able to distinguish lies from truthful statements in a given individual. Although previously scientists could see

"But we can use fMRI to find concealed information. We can ask: Is X individual in terrorist organization Y?"

Politics on the brain: An fMRI investigation

SOCIAL NEUROSCIENCE, 2006, 1 (1), 25–40

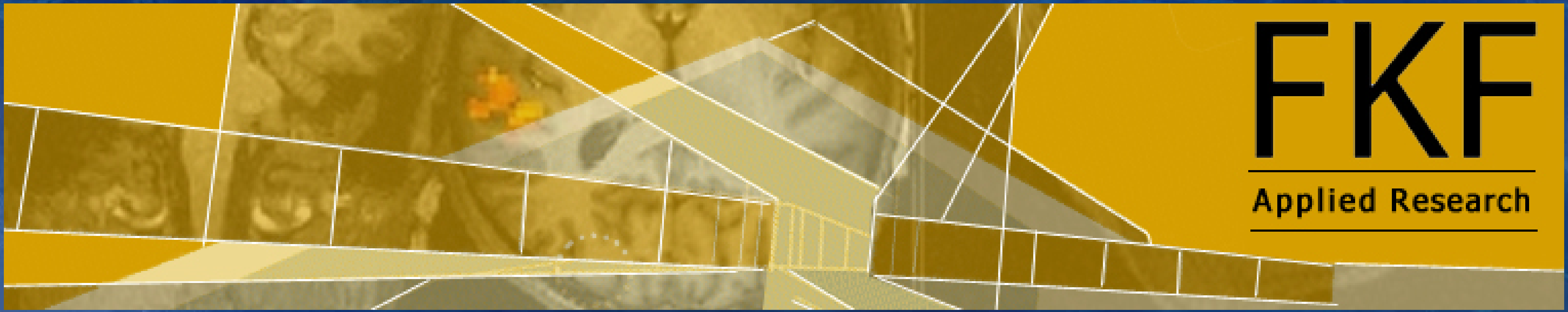
- 30 right handed native English speakers controlled for race and gender were shown faces and names of well-known Democrat and Republican politicians.

TABLE 1
Condition-response mappings in the experiment

Condition	*KEY 1*	*KEY 2*
Congruent condition for Democrat participants OR Incongruent condition for Republican participants	Democrat faces AND Pleasant words	Republican faces AND Unpleasant words
Congruent condition for Republican participants OR Incongruent condition for Democrat participants	Republican faces AND Pleasant words	Democrat faces AND Unpleasant words
Control condition for face task	Faces	Words

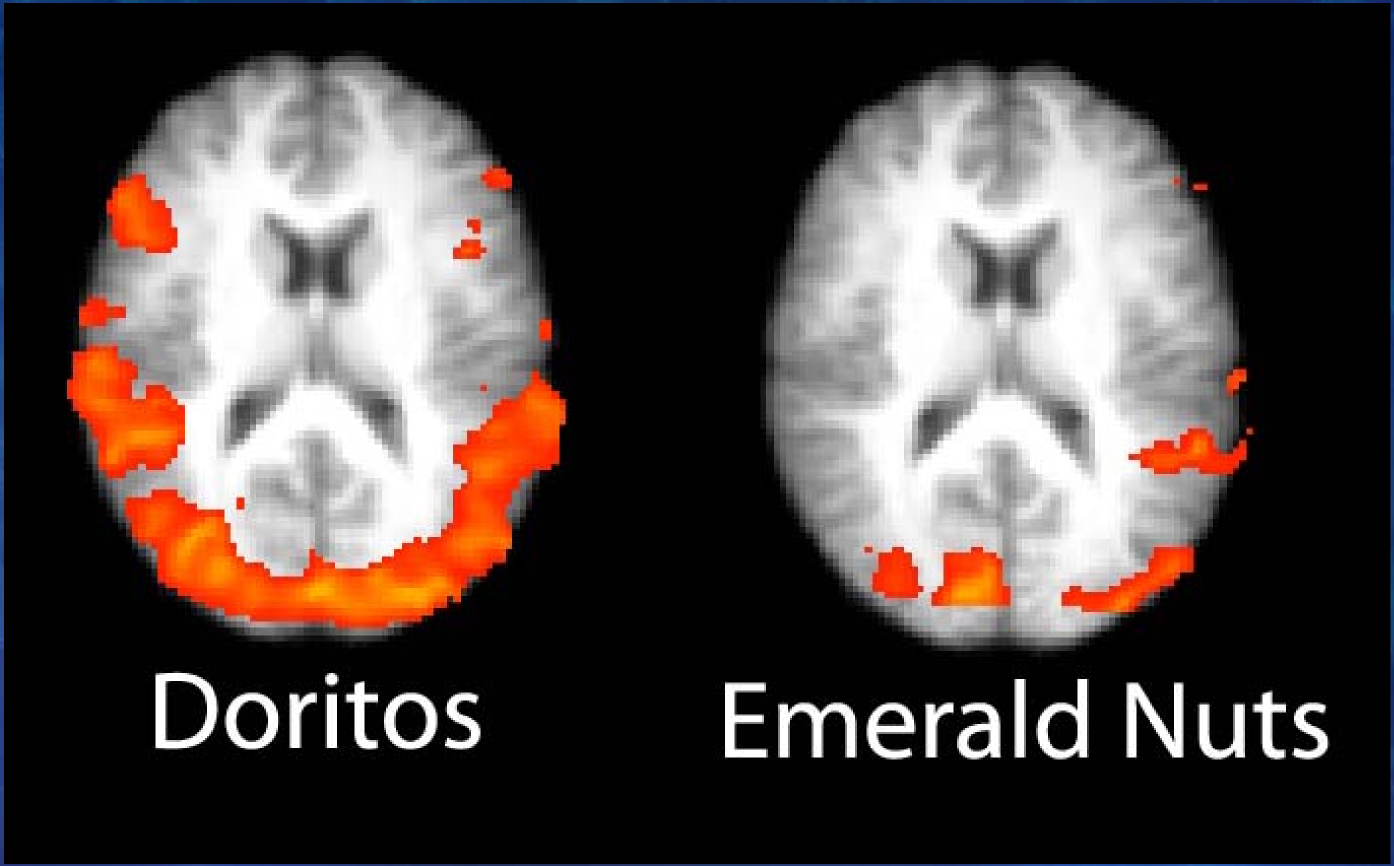
BARROW Neurological Institute

"… help put a bit more science in political science."



fMRI marketing firm started by Clinton and Gore campaign strategists looked at response of Democrat vs. Republican 'brains' to emotionally charged television commercials (Daisy commercial of LBJ vs. 9/11 Bush commercial)

"Neuromarketing" Superbowl XLI: fMRI



New Targets for Psychosurgery

- Lipsman, Neimat, and Lozano. Neurosurgery 61(1):1-13 (2007) reviewed putative targets for surgical treatment of OCD suggested by imaging
  - Volumetric analysis suggests caudate, OFC may be altered in OCD
  - Metabolic studies (PET, SPECT) implicate OFC, cingulate gyrus as well as caudate
  - However, inconsistent and even conflicting data in literature may be attributable to OCD subtypes → imprecise diagnosis

Psychosurgery: Nobel Prize to Public Disgrace and back again?

- John Fulton, Walter Freeman, Egas Moniz invents ‘leukotomy’, publishes first series of 20 pts one year later
  - Moniz awarded Nobel Prize, 1949
- Abuse of procedure, lack of controlled indications, and advent of anti-psychotic medication lead to abandonment of psychosurgical procedures
- Failure of psychosurgery caused ultimately by *inadequate understanding of pathophsyiology of psychiatric disease*

- "…there are those who work in the field of functional imaging of psychiatric disorders who caution against designing surgical interventions based on their findings. However… it is perfectly reasonable that we take the hypothesis that these regions are not merely epiphenomena but rather critical nodes in a network subserving OCD."
  – Ali Rezai, MD

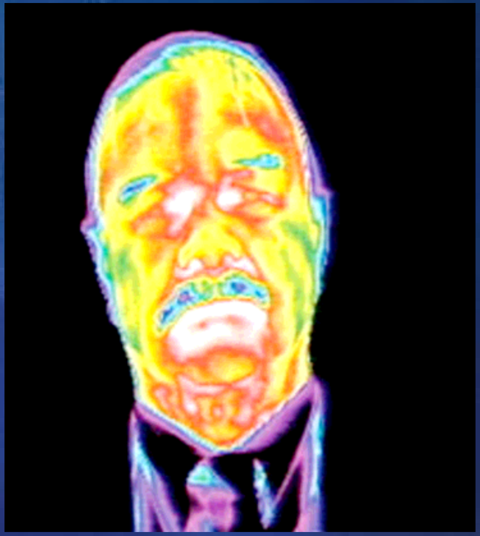
    Director, Center for Neurological Restoration, Cleveland Clinic

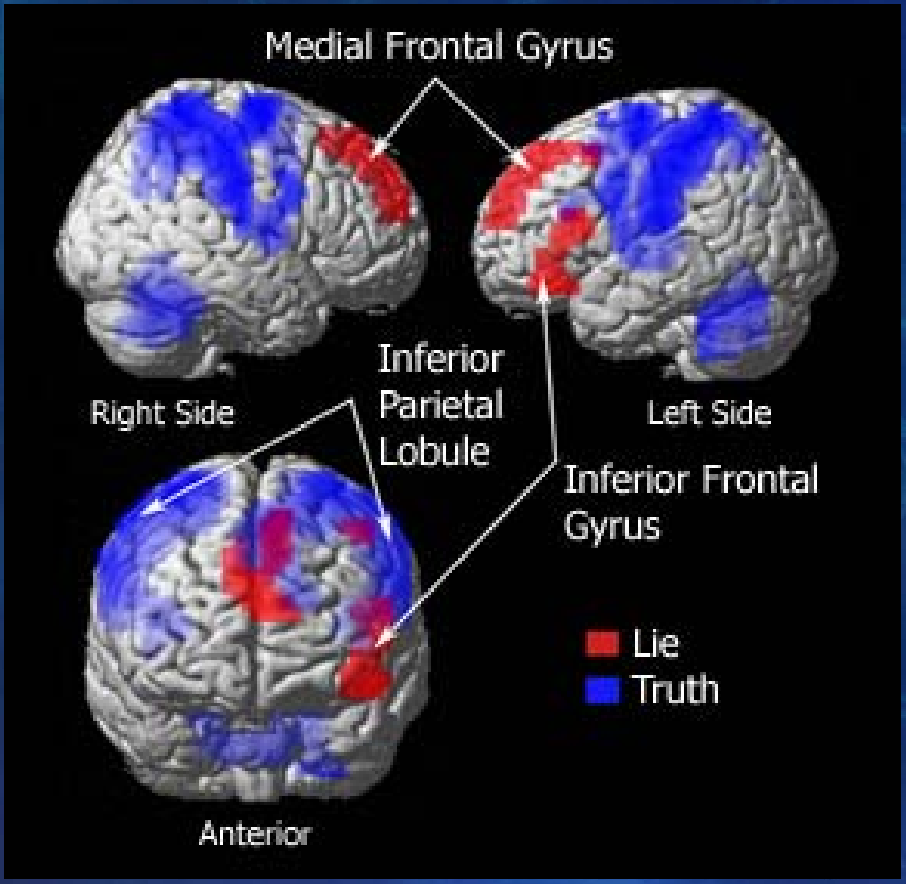
Overview of Ethical Concerns with Neuro-Imaging

1. Premature adoption of technology/ Misapplication
2. Privacy/ Collateral information
3. Forensic use

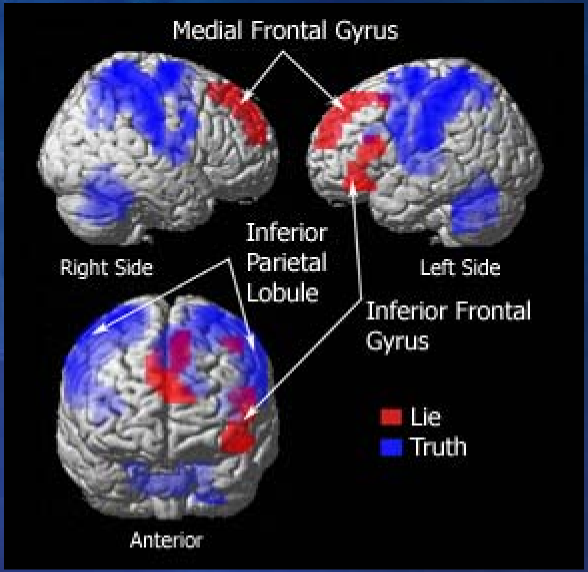
Wople, et al AJOB 5(2): 39-49 (2005)

Deception Detection Technology





Evidence of truthfulness or deceit: Brain imaging or ‘fingerprinting’



Ethics

- **No Lie MRI, Inc. and its franchisees will have and live up to the generally accepted moral and ethical standards of the communities in which it tests. Solutions will be devloped in order to fully realize the beneficial potential of this technology while minimizing the potentially harmful aspects.**
- **Examples of Guidelines For Testing**
- **Testing will only be conducted with the full consent of the interviewee**
- **Testing will only be done on those topics the individual being tested agrees to in advance**
- **Legal**
- **No Lie MRI, Inc. is presently working to have its testing allowed as evidence in U.S. and State courts. Applicable laws depend on the country and jurisdiction involved.**

http://www.noliemri.com/index.htm

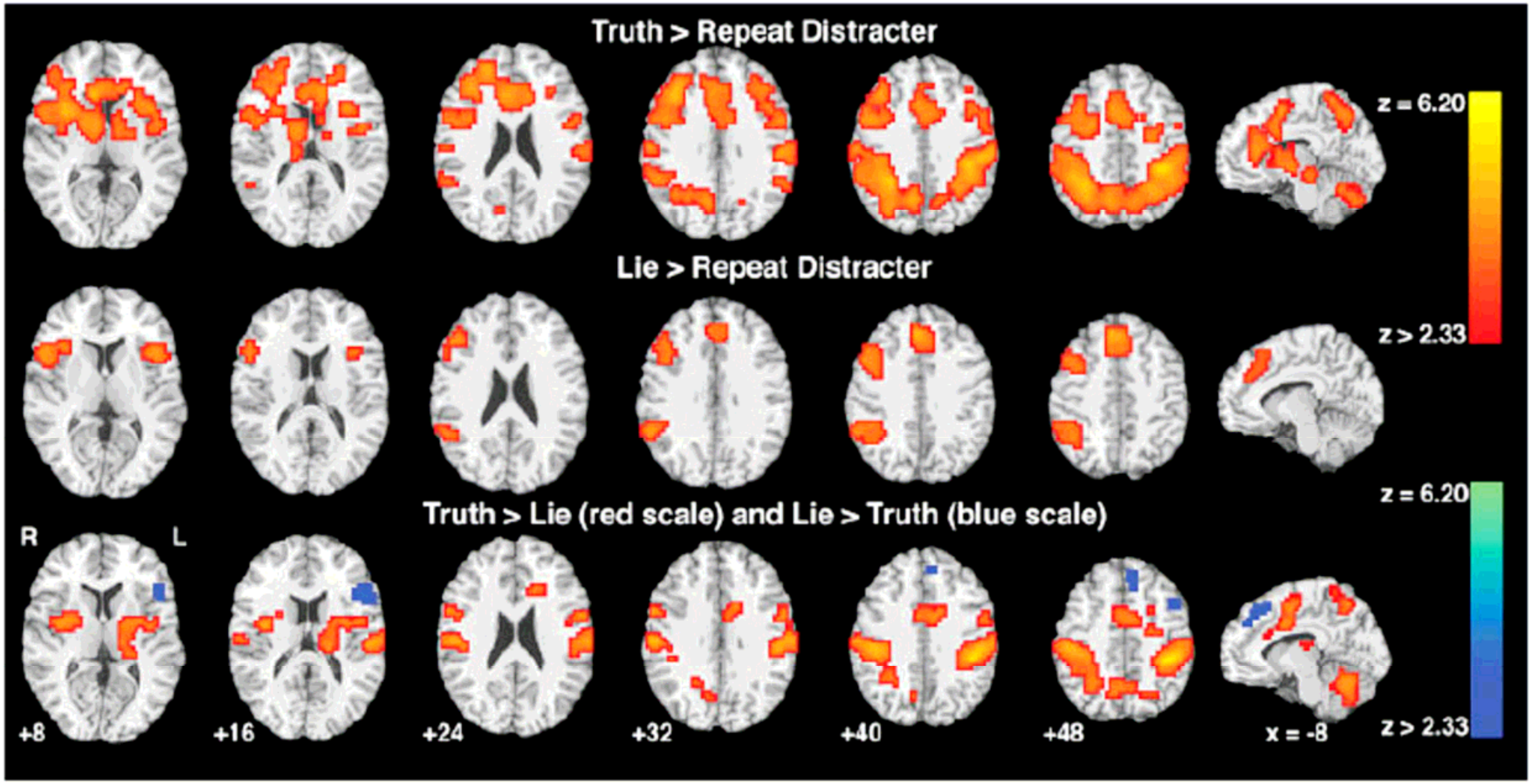


Figure 1.

Group analysis (n = 22) showing significant differences in brain activation between Lie, Truth, and Repeat Distracter conditions. Row 1: Truth > Repeat Distracter; row 2: Lie > Repeat Distracter; row 3: Lie > Truth (blue scale) Truth > Lie (red scale). Images are displayed over a Talairach-normalized template in radiological convention. Significance thresholds for all contrasts based on spatial extent using a height of $z \geq 2.57$ and cluster probability $P \leq 0.05$, except Lie > Truth (blue scale) presented at a $z \geq 1.64$, uncorrected. See Tables 2–4 for anatomical localization.

Daniel D. Langleben,* James W. Loughead, Warren B. Bilker, Kosha Ruparel, Anna Rose Childress, Samantha I. Busch, and Ruben C. Gur

University of Pennsylvania, Philadelphia, Pennsylvania

- Ought there to be constitutional protection for compelled neuro-imaging data?
  - Polygraph
    - EPPA: Cannot be used in civil hiring context
    - Exemption for government employees
  - IAT testing: personality screening paper and pencil tests are already commonly in use
  - Is there an inherent privacy right in cognitive data?
  - 4^{th} and 5^{th} amendment protections?

Overview of Ethical Concerns with Neuro-Imaging

1. Premature adoption of technology/ Misapplication
2. Privacy/ Collateral information
3. ***Forensic use***

Wople, et al AJOB 5(2): 39-49 (2005)

Harrington v. Iowa

- ‘Brain fingerprinting’
  - the ‘P300/ MERMER’ event related potential
  - distinguish subjects recognition of known vs. novel stimuli
- No peer review
  - has been introduced as evidence in criminal proceedings (Harrington v. Iowa)
- Wider adoption will depend on particular rules courts use to determine whether evidence is sufficiently ‘scientific’ to be admitted as evidence

Court Ordered Treatment: Sell v. US

- The Sell Test
  1) Facing serious charges
  2) Treatment is medically appropriate
  3) Substantially unlikely to have side-effects that the might undermine fairness
  4) No less intrusive alternatives
  5) Necessary to further important government trial-related interests

- CFR Sec 549.43 (2002) involuntary medication may be given if psychiatrist determines it is necessary “in order to attempt to make the inmate competent for trial….”

- Question: What is the role of more invasive therapies in the treatment of incompetent persons?

  If treatment of Sell required brain surgery, would outcome of case be different?

Conclusions

- Advances in imaging are yielding insights into brain physiology that are widely applicable beyond pre-surgical planning or academic brain mapping
- Standards of review for use of such data is high for scientific and medical purposes, lower for legal purposes, and ?non-existent for commercial ones
- Awareness of potential un-intended consequences of neuro-imaging research will help prevent or curb abuses

Challenges and Opportunities for MRI in Traumatic Brain Injury

Mark Cohen

UCLA

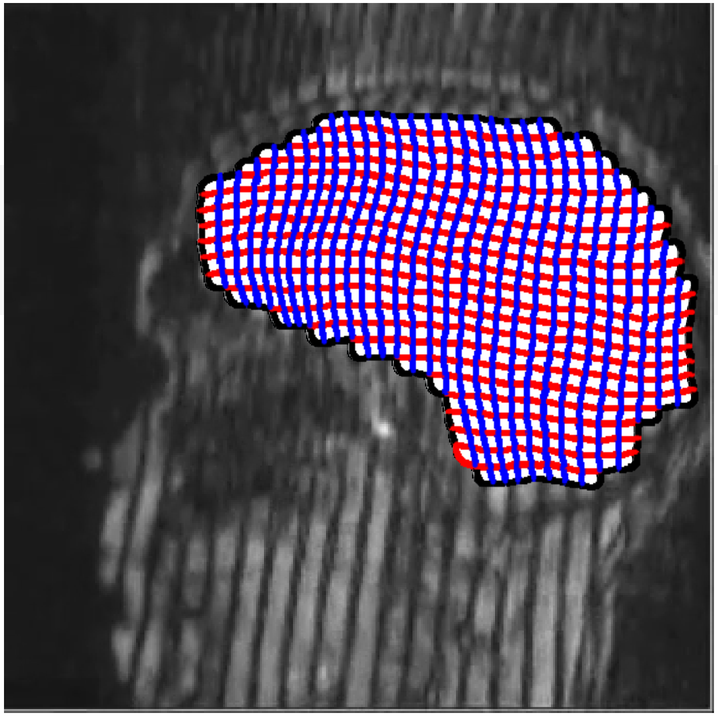
Psychiatry, Neurology, Radiology,

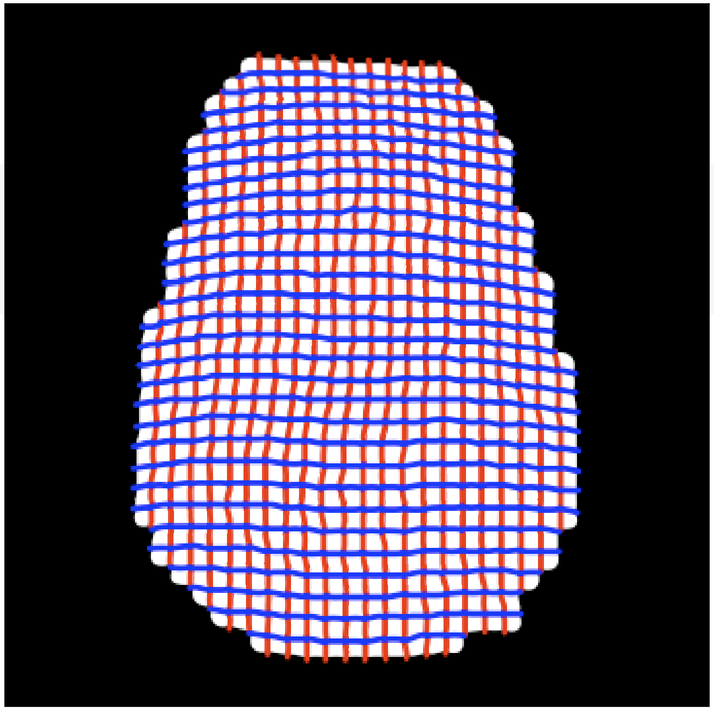
Biomedical Physics, Psychology

Imaging Needs in TBI

- Basic Mechanisms & Research
- Acute Triage
- Disease Progression
- Functional Assessment
- Treatment Efficacy Assessment
- (functional) Image Guided Therapy

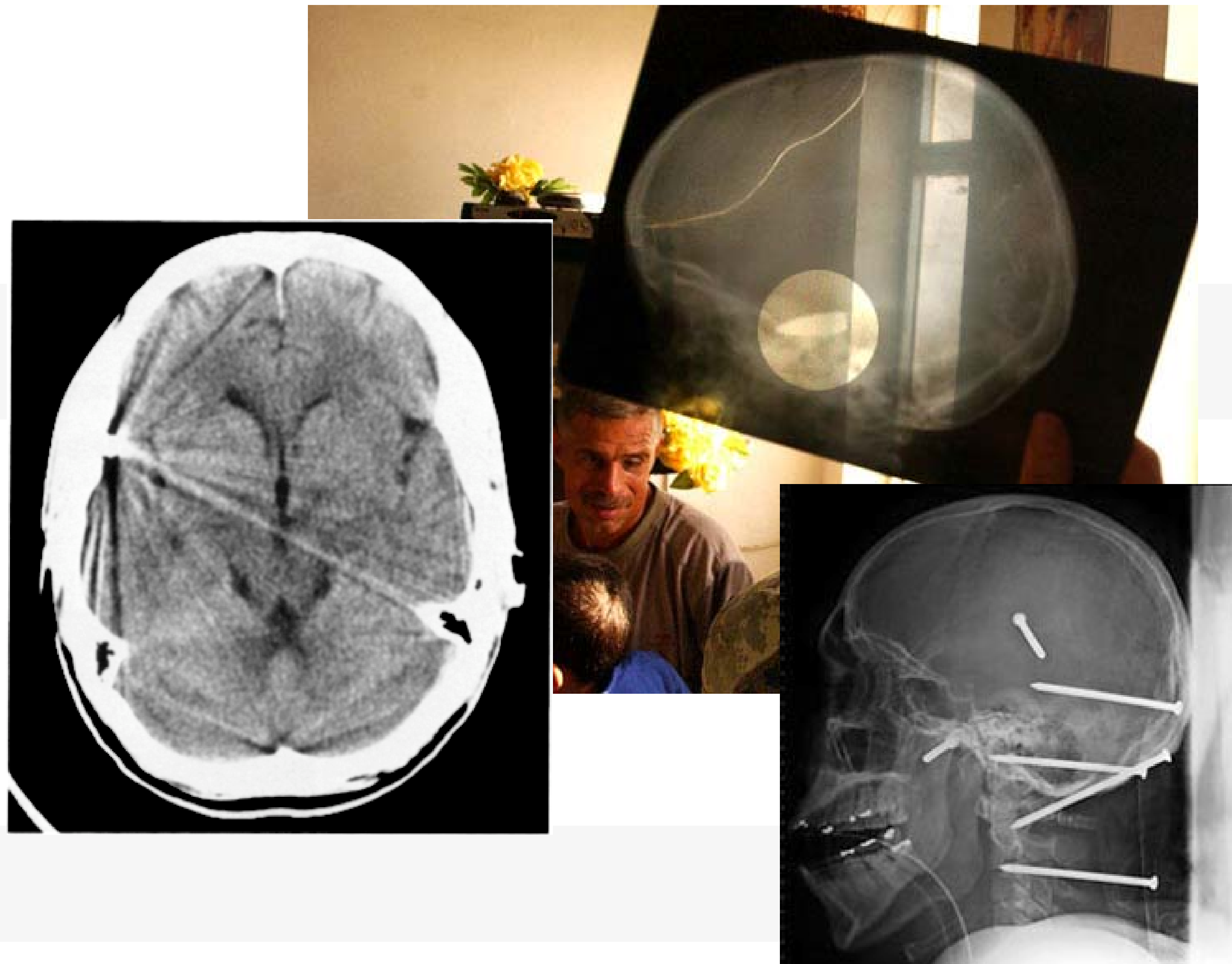
Head Injury Mechanisms…





Courtesy of Philip Bayly
Washington University in St. Louis

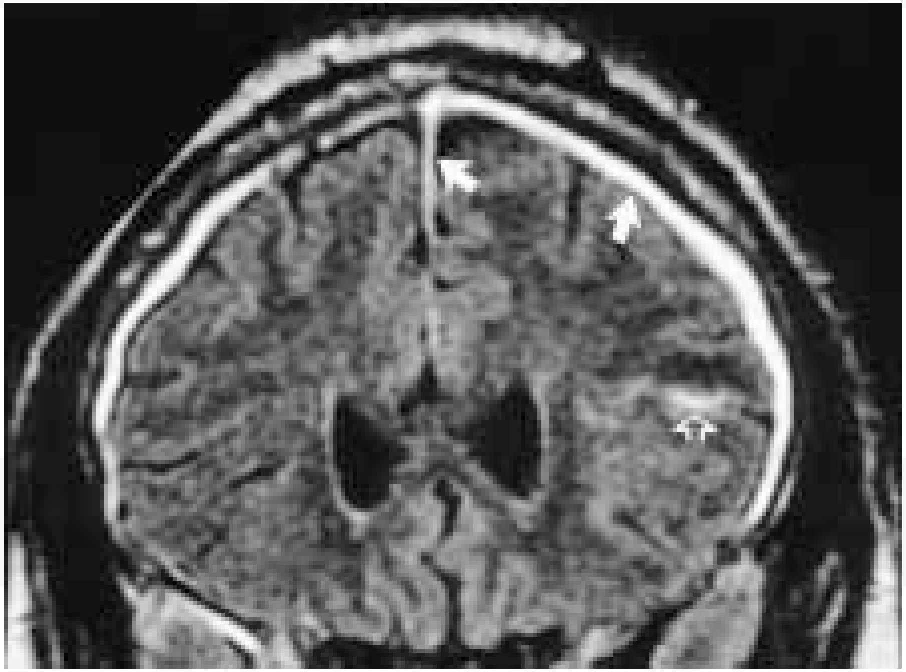
CT vs. MRI in Traumatic Brain Injury



Shrapnel is an *a priori* Hazard in High Field MRI

CT vs. MRI in Traumatic Brain Injury

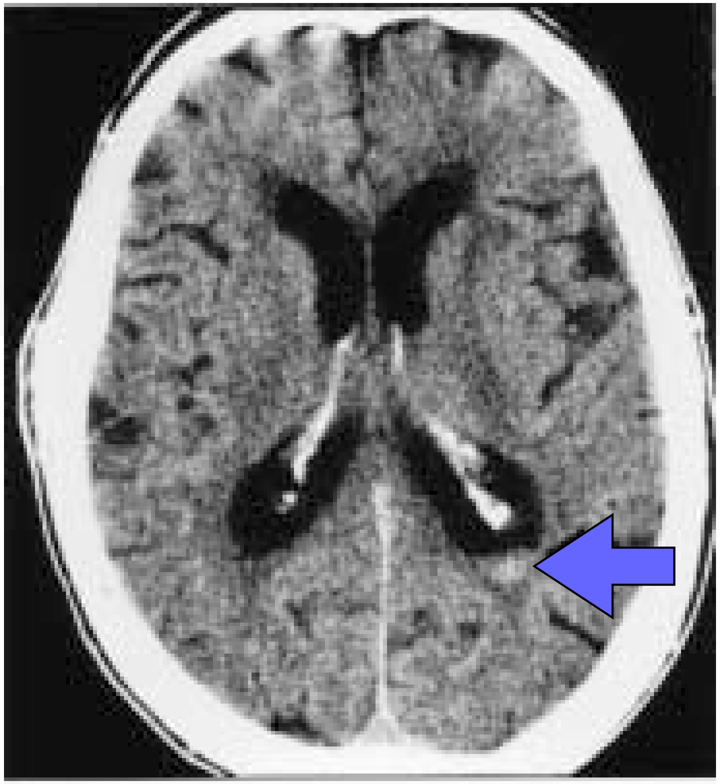
- Acutely, both CT and MRI Show Subarachnoid Hematoma well
- CT findings tend to normalize subacutely, but remain visible on MRI

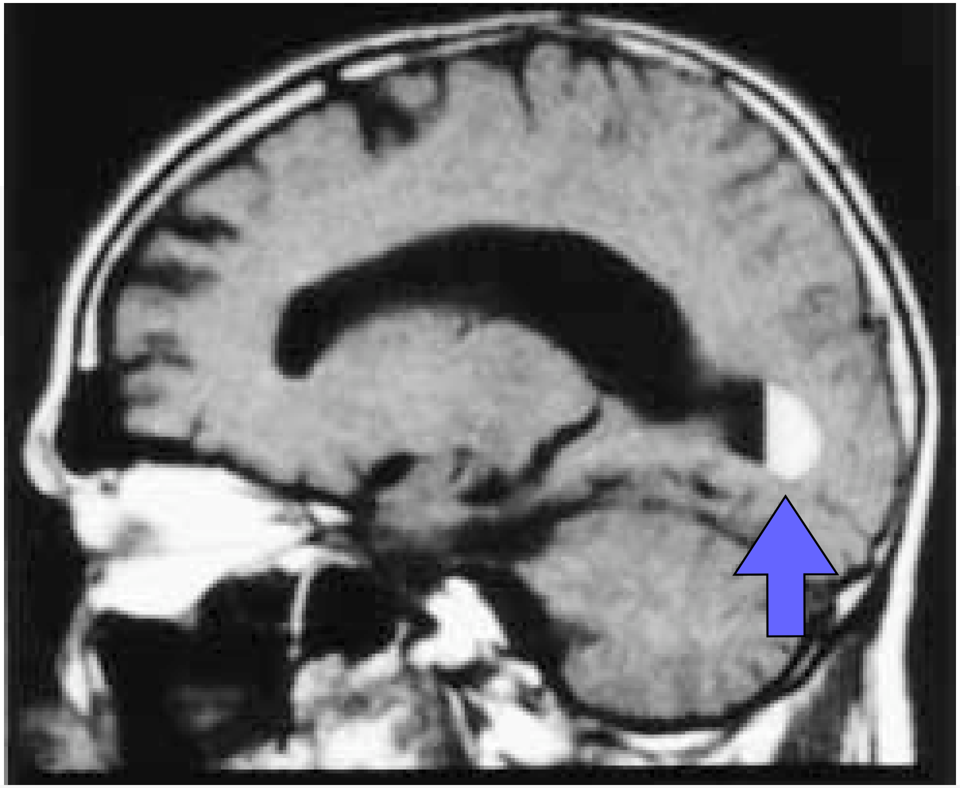


C. M. Glastonbury, and A. D. Gean
SEMINARS IN NEUROSURGERY 14, 2003

CT vs. MRI in Traumatic Brain Injury

- Intraventricular Hemorrhage





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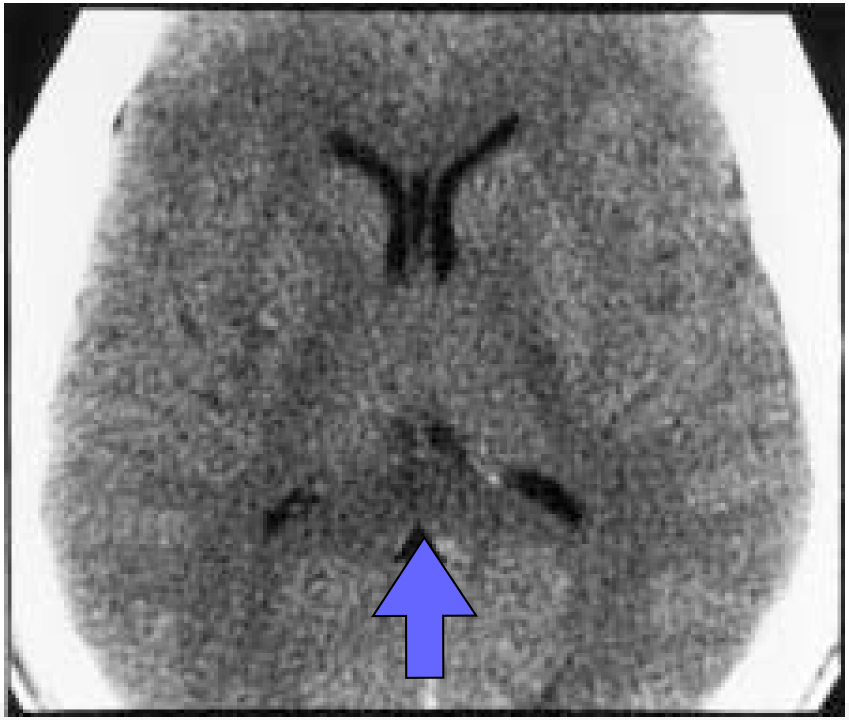

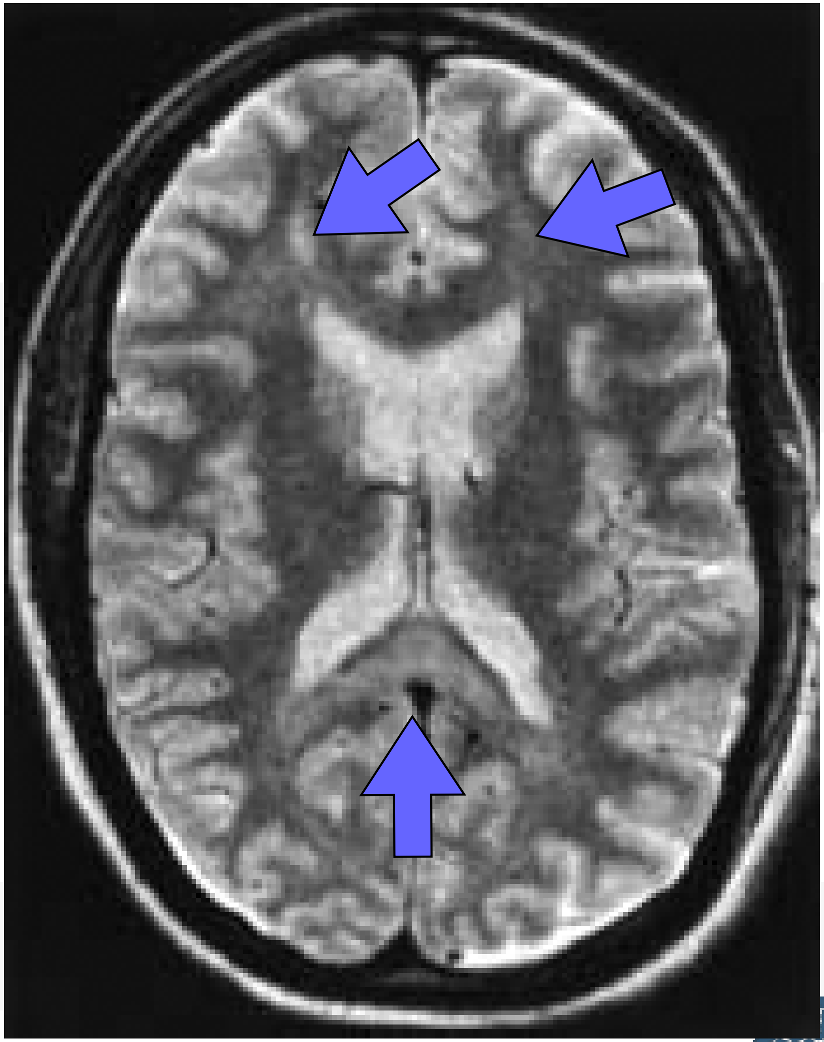

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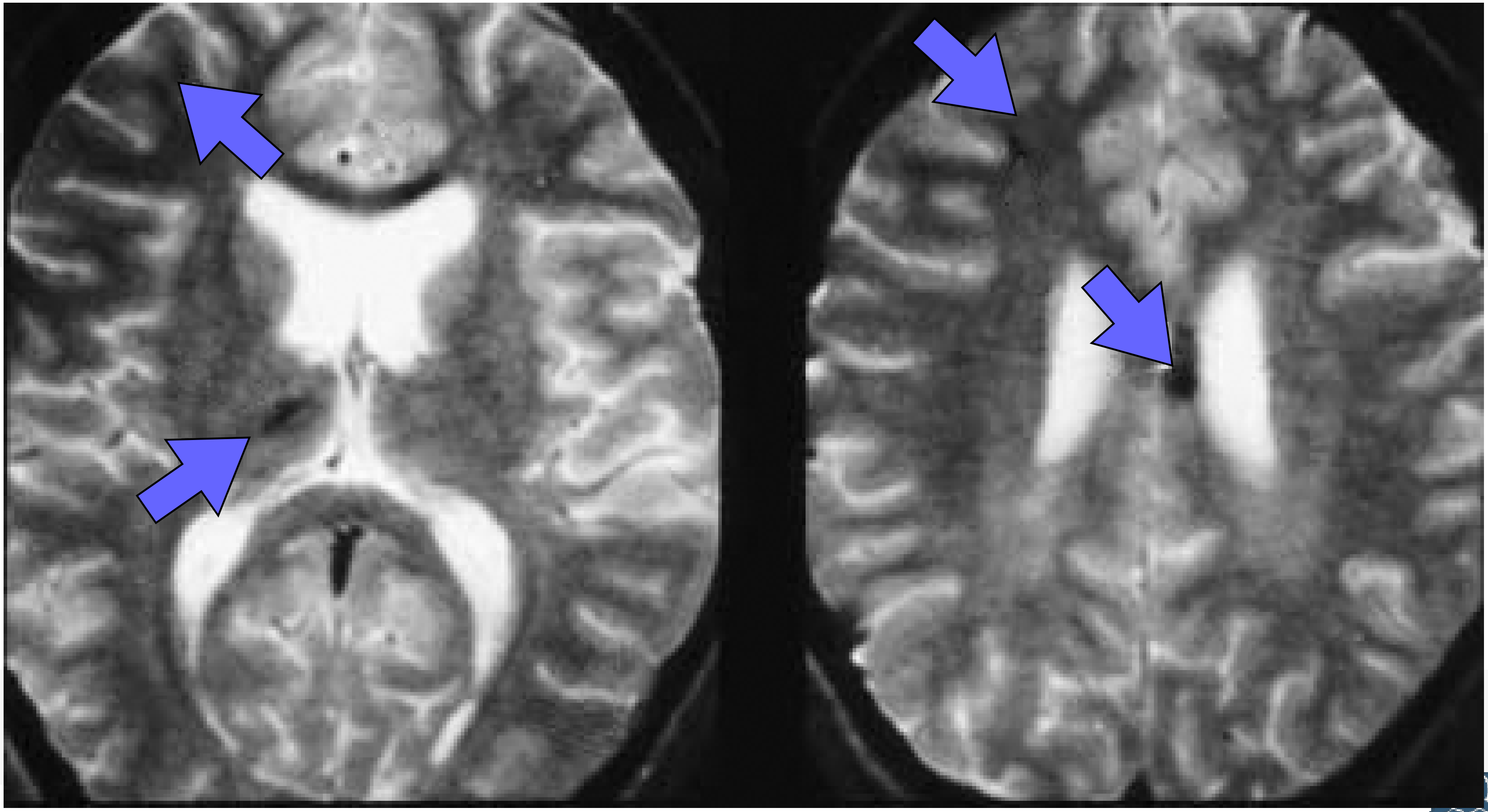
SEMINARS IN NEUROSURGERY 14, 2003

CT vs. MRI in Traumatic Brain Injury



C. M. Glastonbury, and A. D. Gean
SEMINARS IN NEUROSURGERY 14, 2003

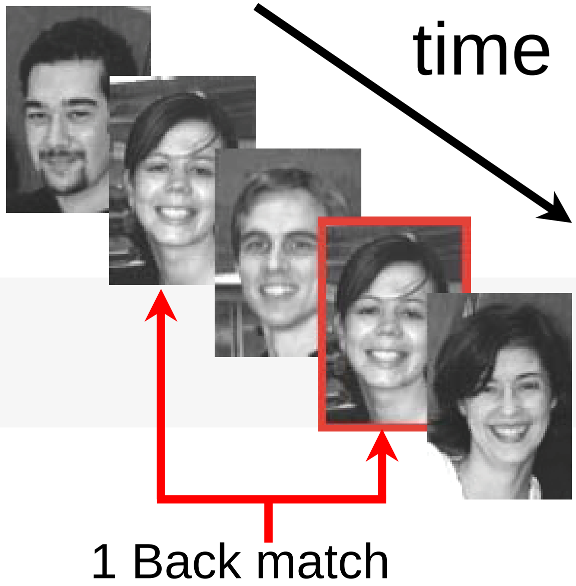
MRI in Traumatic Brain Injury

C. M. Glastonbury, and A. D. Gean
SEMINARS IN NEUROSURGERY 14, 2003

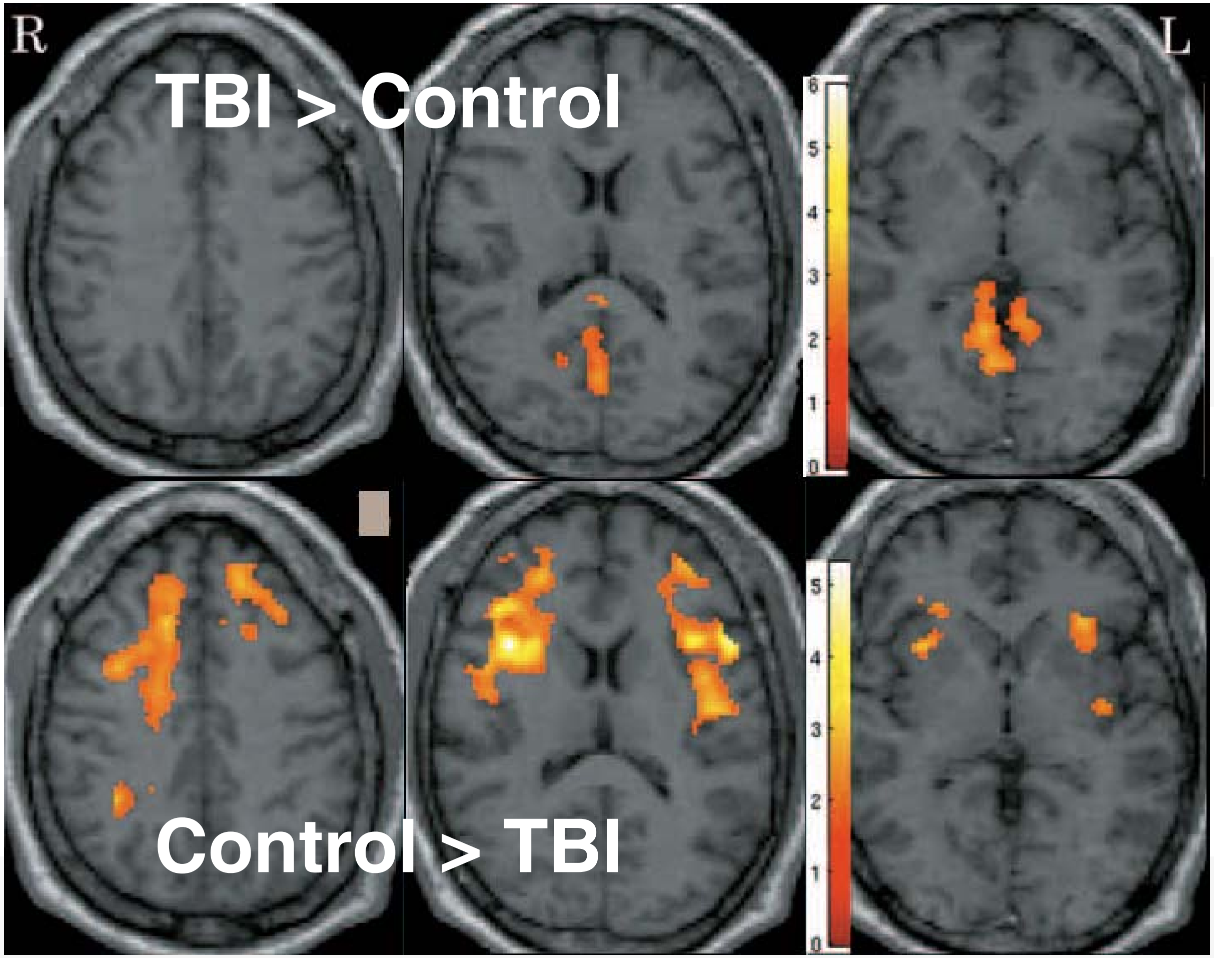
MRI in Traumatic Brain Injury

Ultra Low Field MRI Might Supplant the Use of CT in MRI, As the Risk and Cost are Reduced Greatly, While Offering Improved Sensitivity and Specificity

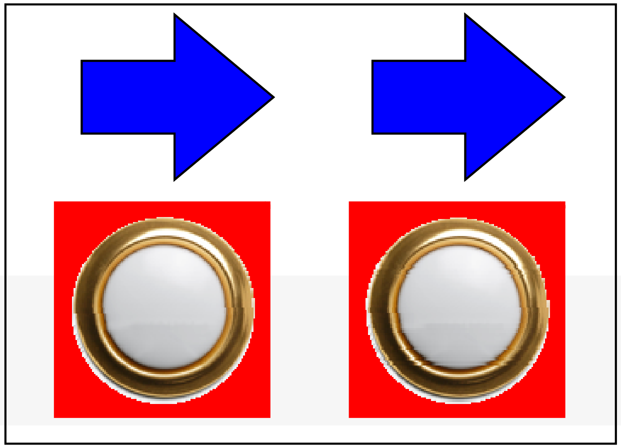
Functional Assessment



Significant Group Differences only for 1-Back Only
(*not 0-Back or 2-Back*)

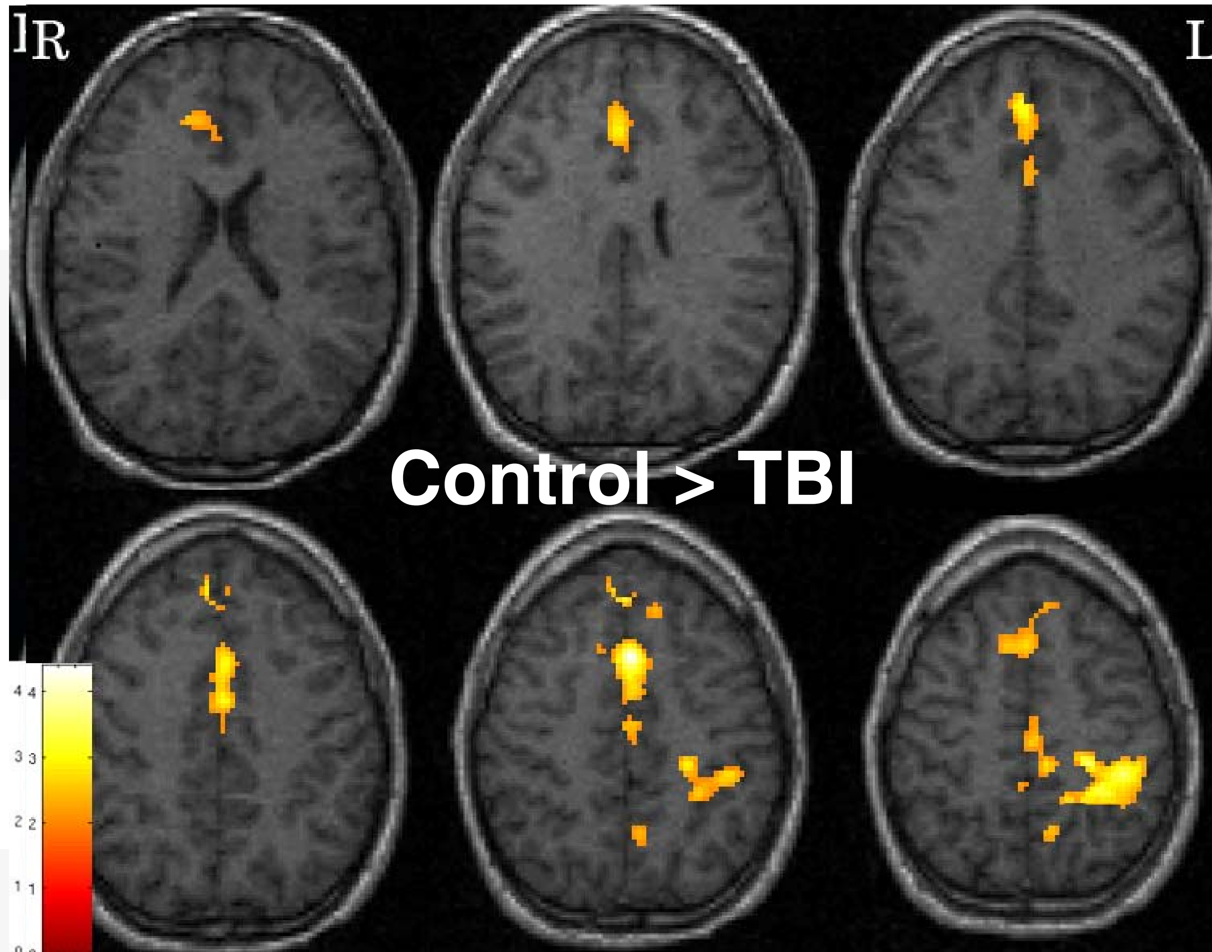


Functional Assessment



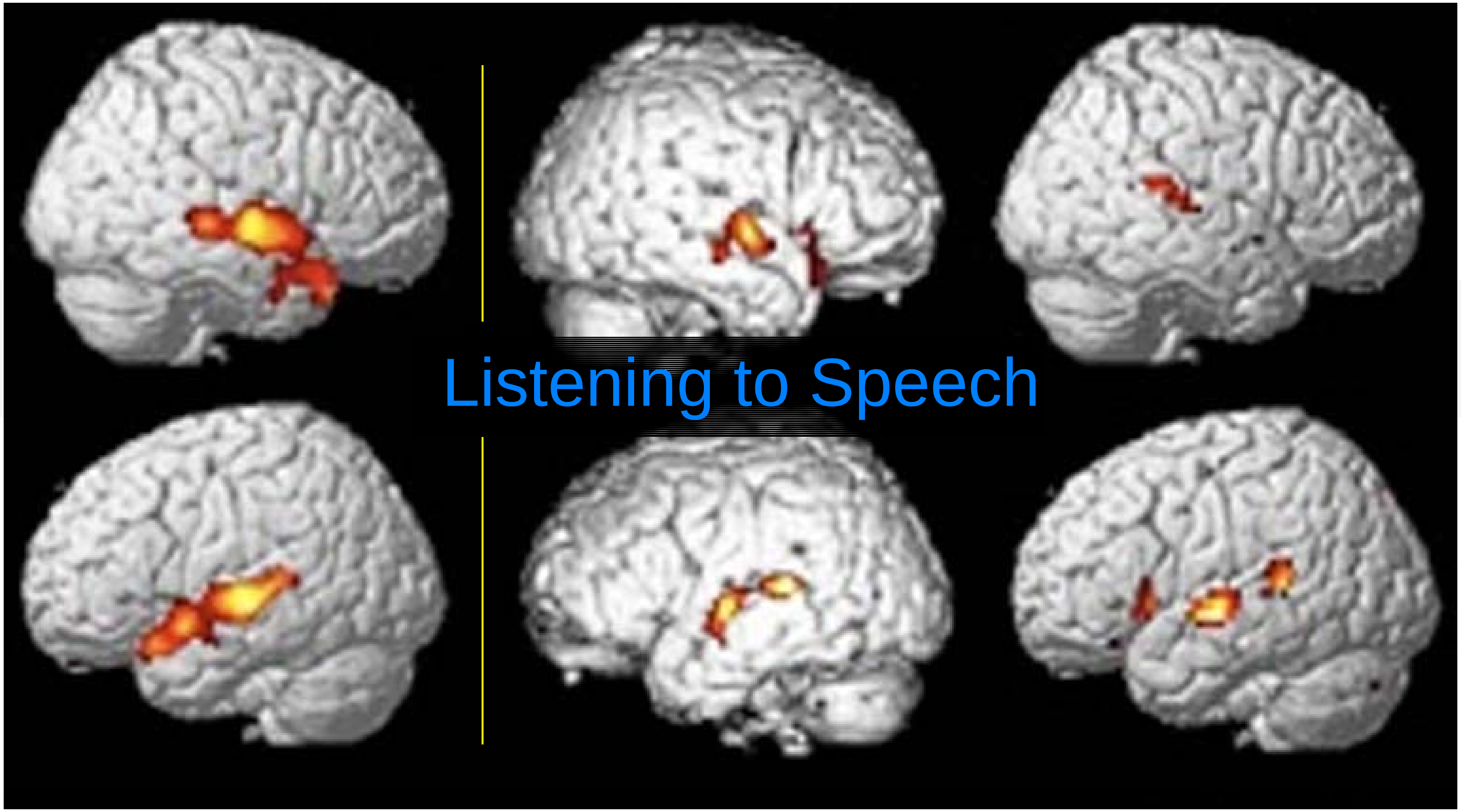
Controls showed Increased activity in Incompatible Trials

TBI Patients Showed Stronger Correlation with Accuracy



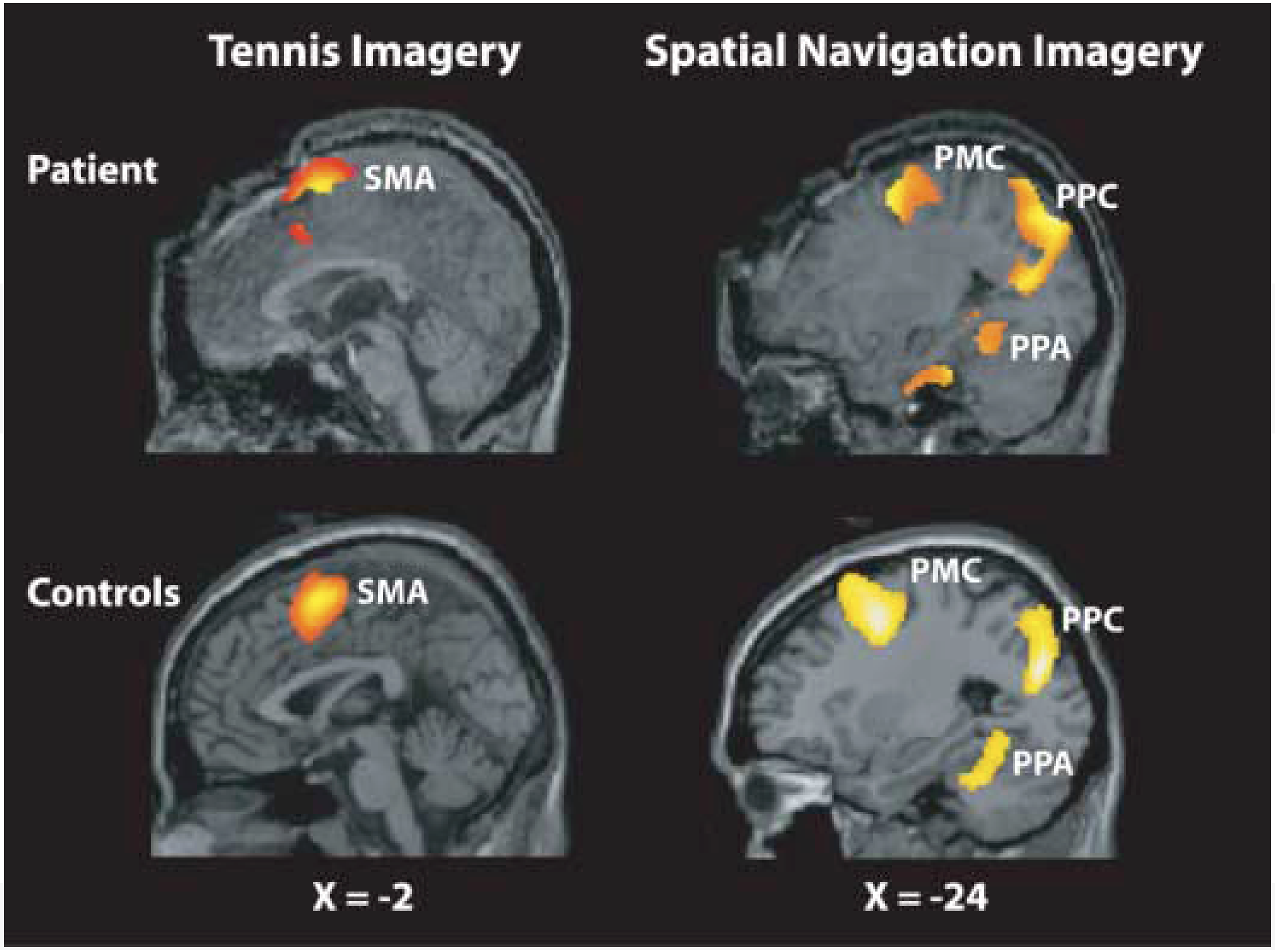
R. S. Scheibel, *et al.*, Neurorehabilitation and Neural Repair 21, 2007

Detection of Cognitive Awareness



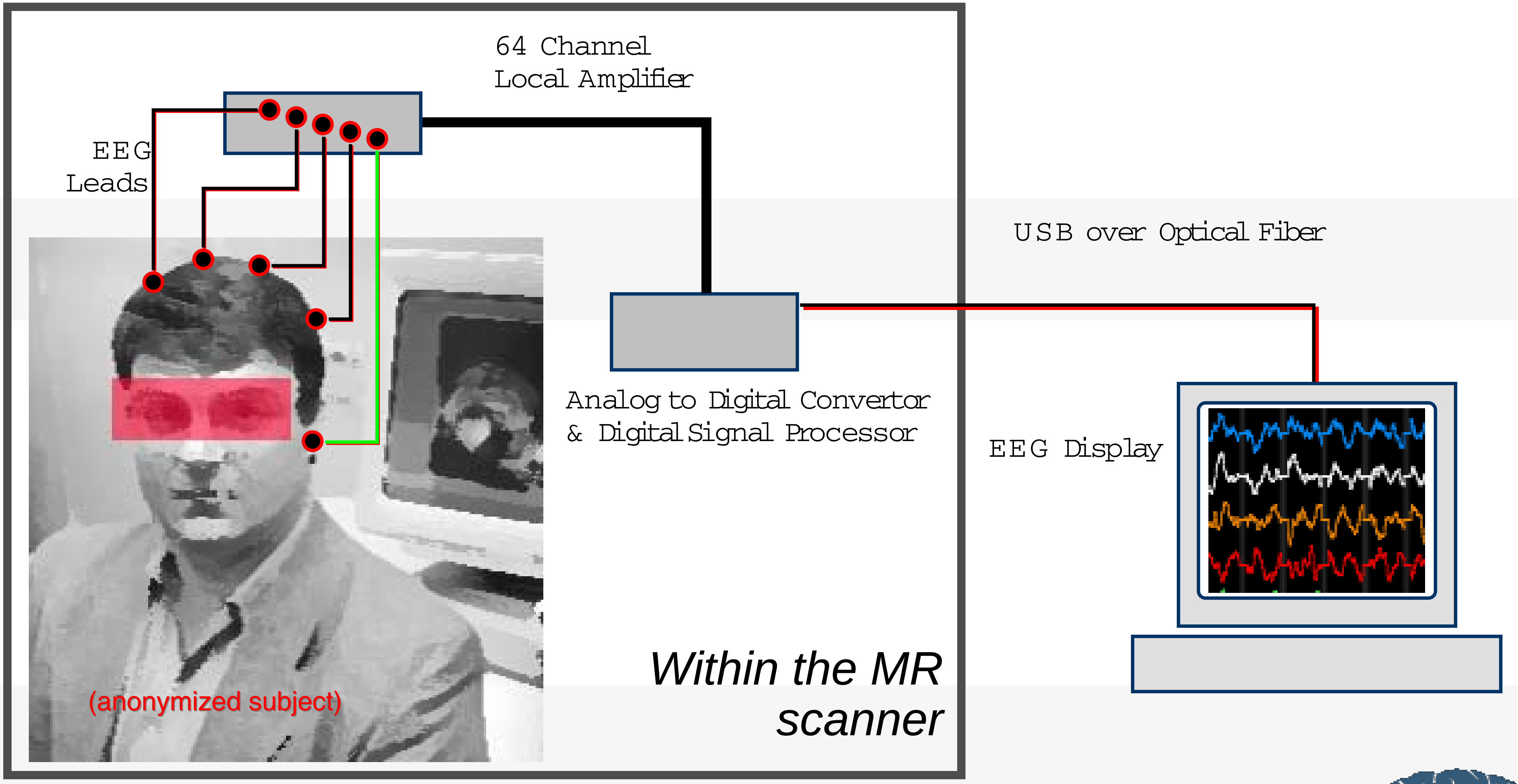
Healthy Volunteer	Vegetative State	Vegetative State

Detection of Cognitive Awareness



A.M. Owen, *et al.*, Science 313, 2006

MRI-Compatible EEG System Design



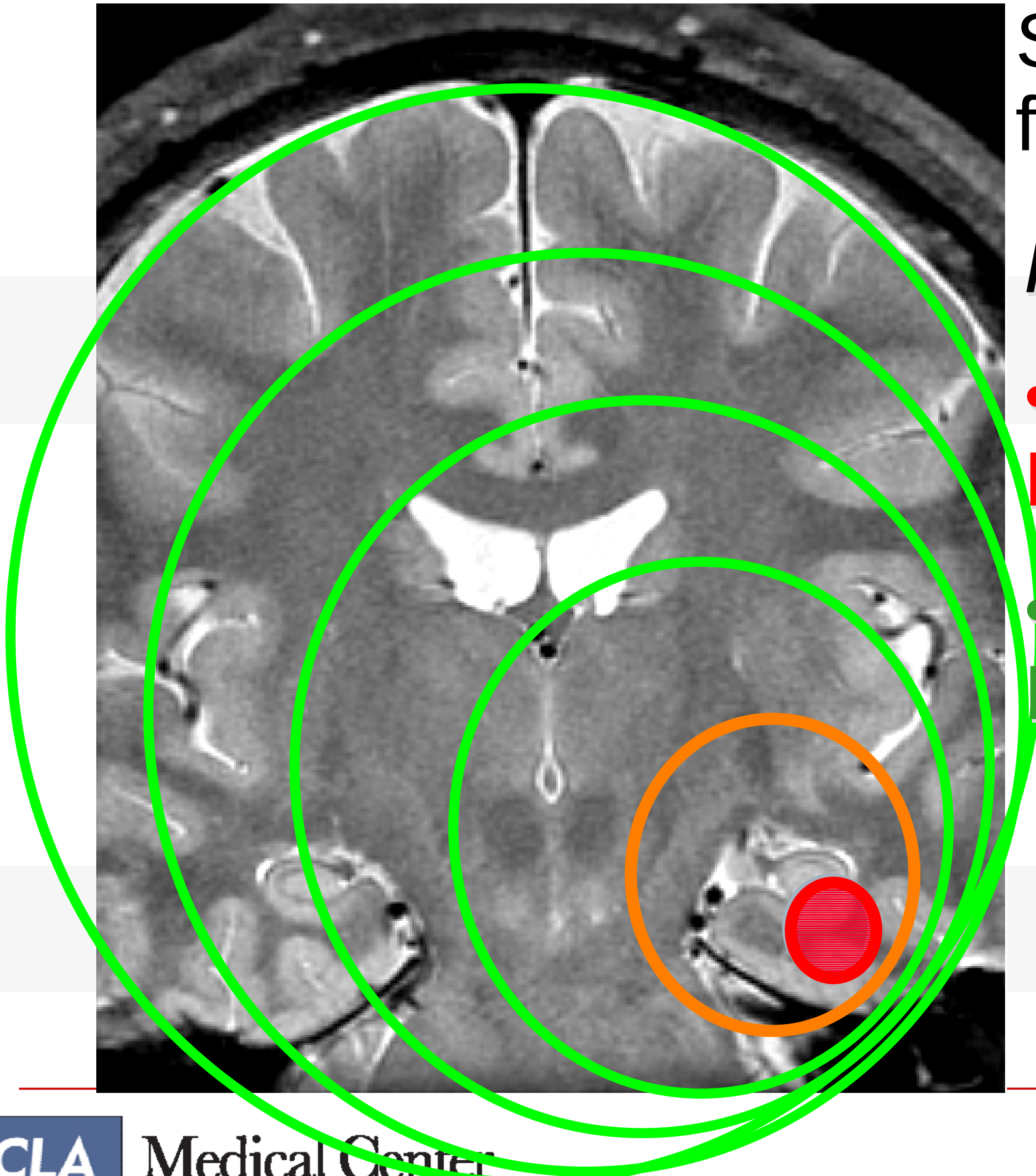
Epilepsy and TBI

"Studies suggest that about **20 to 25 percent** of individuals with "closed-head" brain injuries **will go on to develop … post-traumatic epilepsy** (PTE). The only study that has investigated the prevalence of PTE in the military, reported in 1985, found that **as many as 50 percent of Vietnam veterans** who had suffered penetrating brain injuries during combat **developed seizure disorders months or years later**."

EPILEPSY FOUNDATION®
Not another moment lost to seizures™

http://www.epilepsyfoundation.org/epilepsyusa/tbi-special-report.cfm

Red and Green Spikes



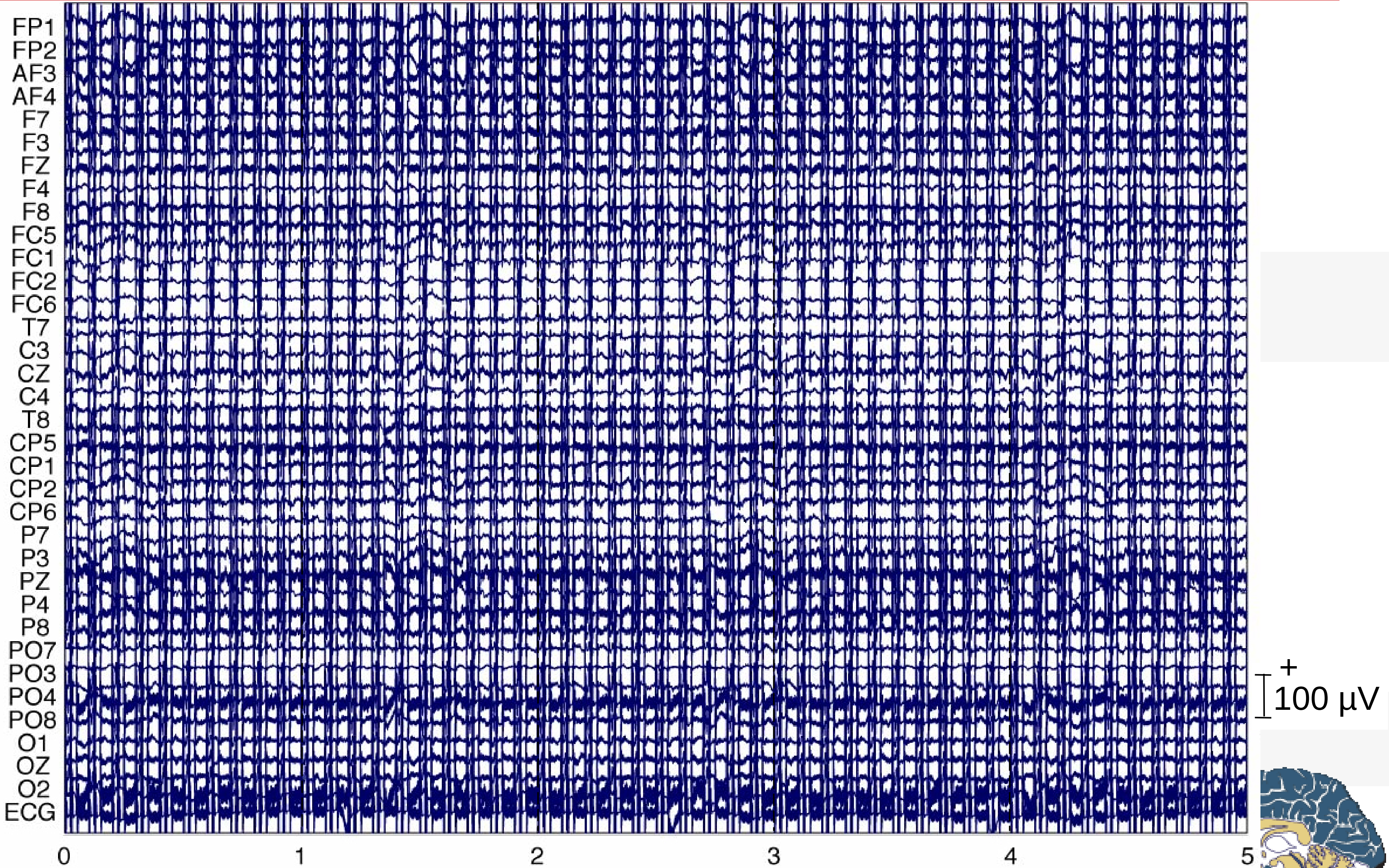
Seizure Activity Spreads from an Irritative Zone

Hypotheses:

- Initial Event is Energetically Costly
- Spreading Depolarization is Not

Functional MRI may be timed by Epileptiform Spikes

Artifact Mediation



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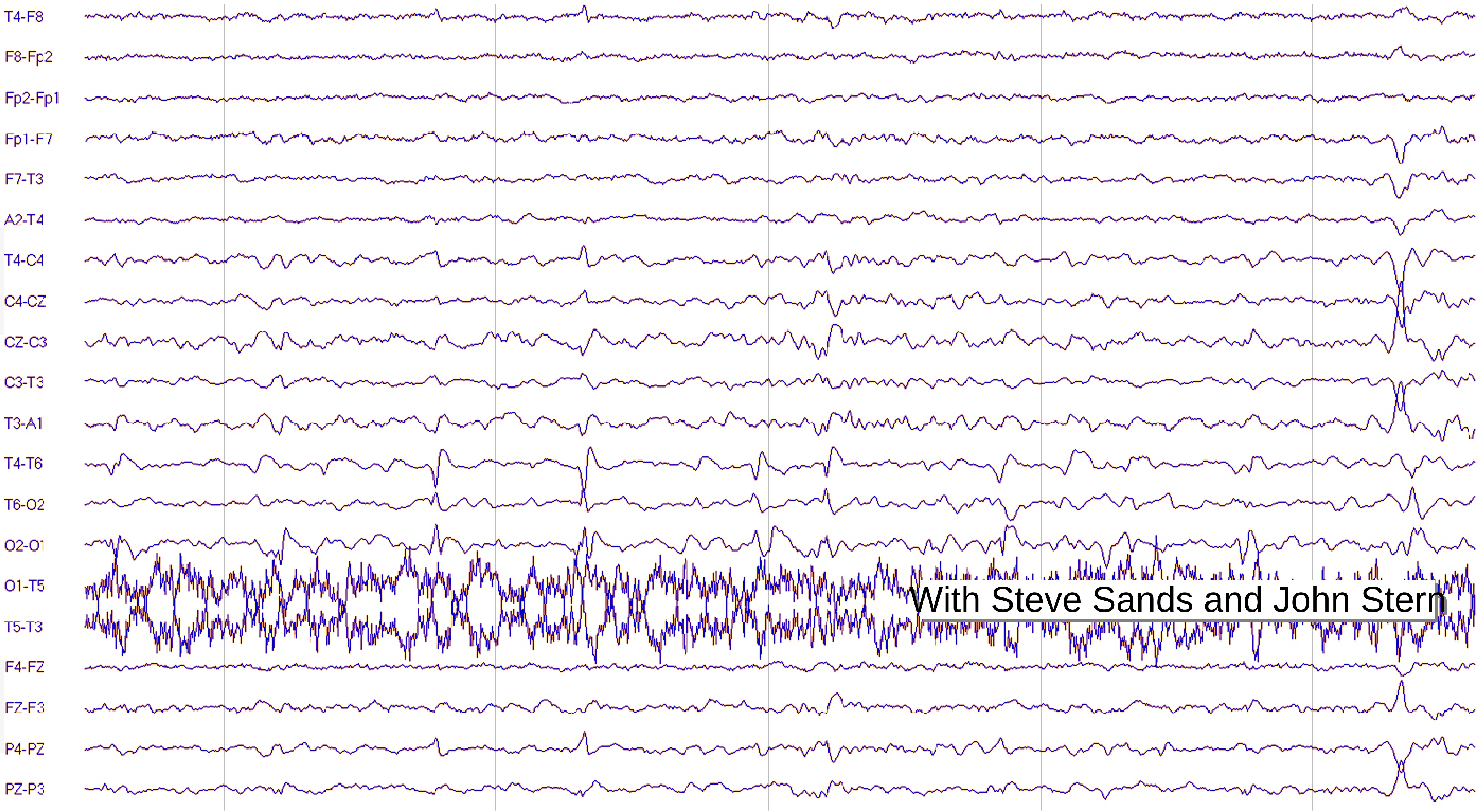
Interictal Discharge



With Steve Sands and John Stern

100 µV

1 sec

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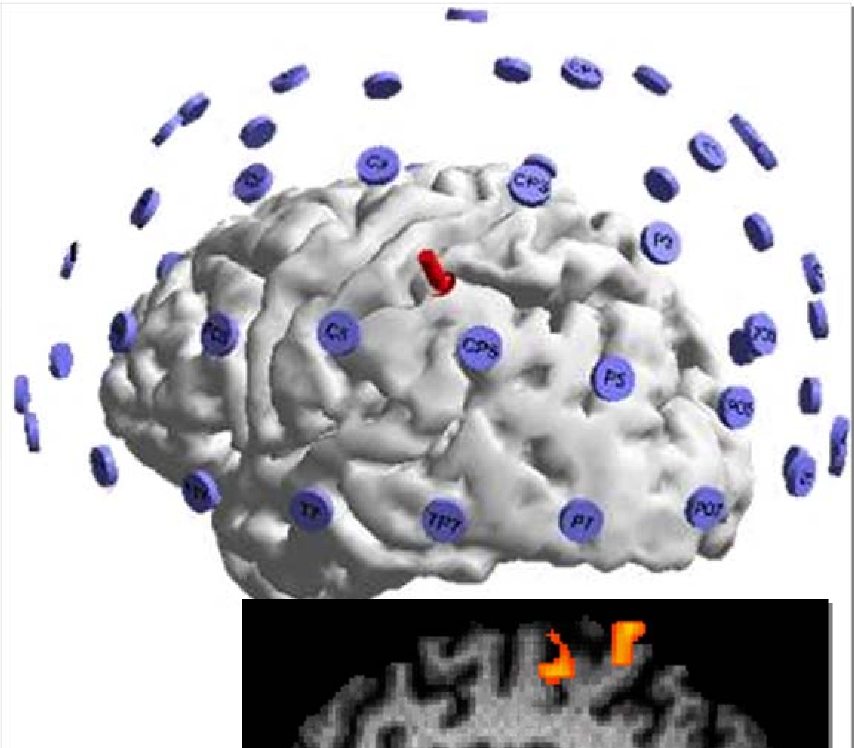
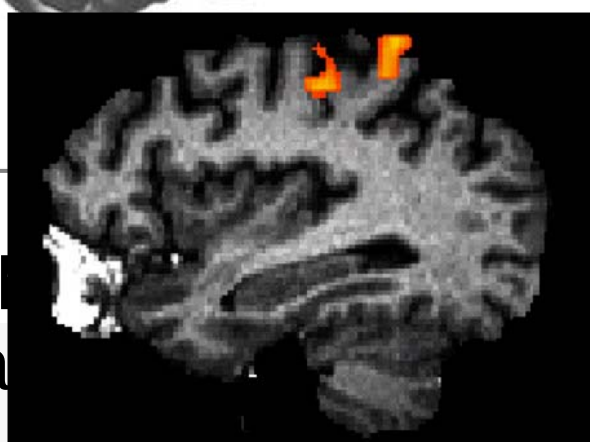
IED Time Course

QuickTime™ and a
YUV420 codec decompressor
are needed to see this picture.

with
John Stern
Alex Korb
Manjar Tripathi
Massoud Akhtari

Somatosensory Evoked Potentials





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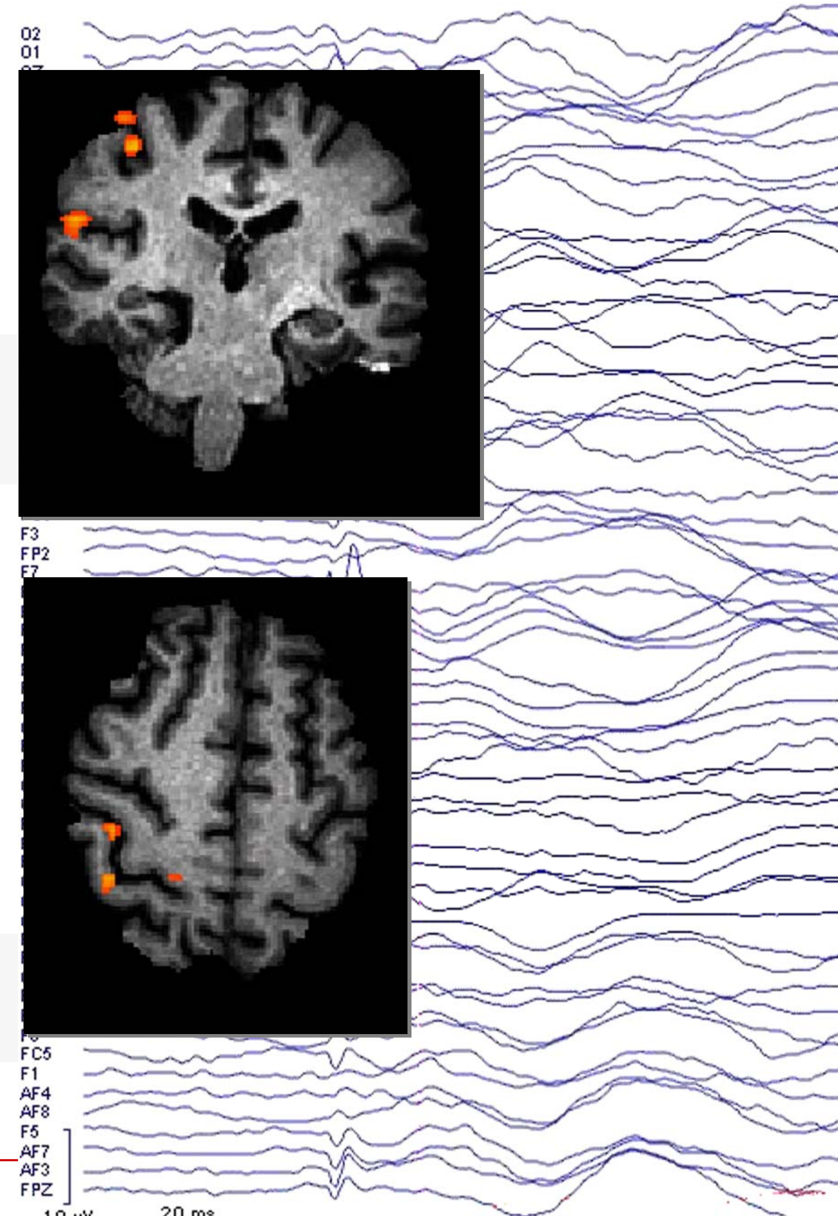

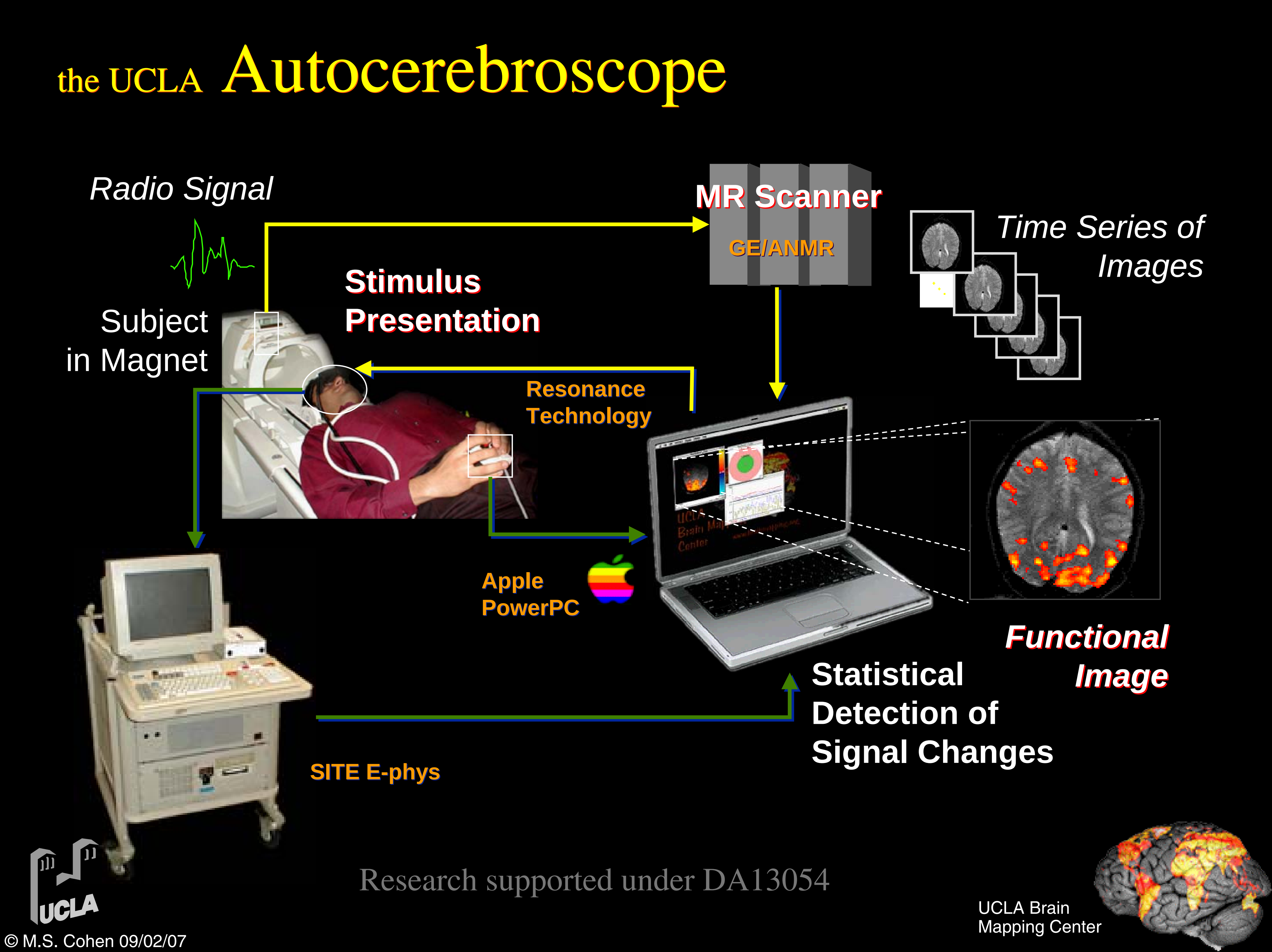
the UCLA Autocerebroscope
Radio Signal
MR Scanner
GE/ANMR
Time Series of Images
Stimulus Presentation
Subject in Magnet
Resonance Technology
Apple PowerPC
UCLA Brain Mapping Center
Functional Image
Statistical Detection of Signal Changes
SITE E-phys
UCLA
Research supported under DA13054
UCLA Brain Mapping Center
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SHORT-TERM TRAINING PROTOCOL in HEALTHY SUBJECTS

Omneuron

ROI TARGET:

Rostral Anterior Cingulate cortex.

CYCLE, (3 blocks, 150s total)

BLOCKS

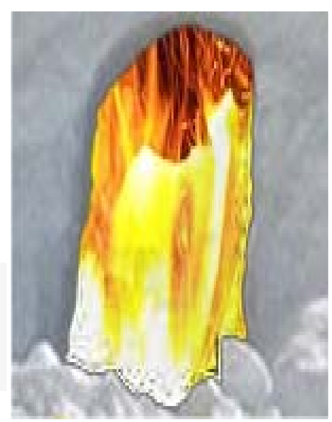
Rest 30s	Increase 60s	Decrease 60s
	Pain	Pain

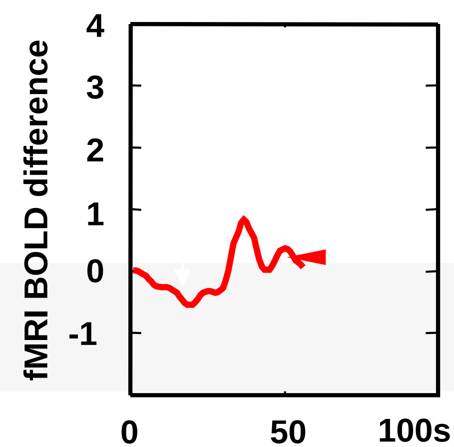
RUNS

Briefing
Pre-Tests
Anatomicals

Cycle 1 150s	Cycle 2 150s	Cycle 3 150s	Cycle 4 150s	Cycle 5 150s	After Scan Ratings	Debrief

RUN, (5 cycles + ratings, 13min). 1-5 **RUNS** per **TRAINING DAY**)





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C. deCharms, et al.,
PNAS, 102, 2005

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Training Effects on fMRI Signal

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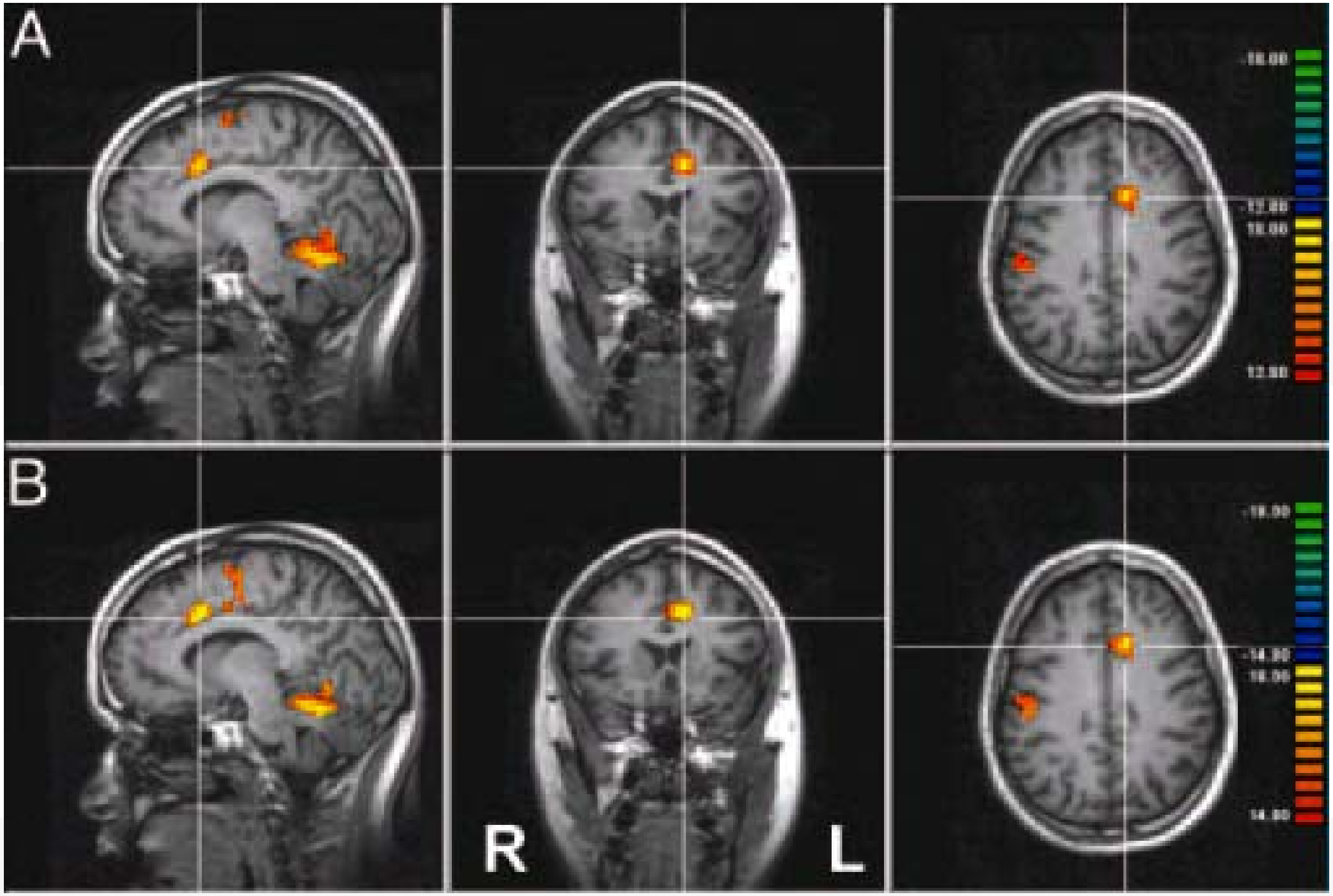
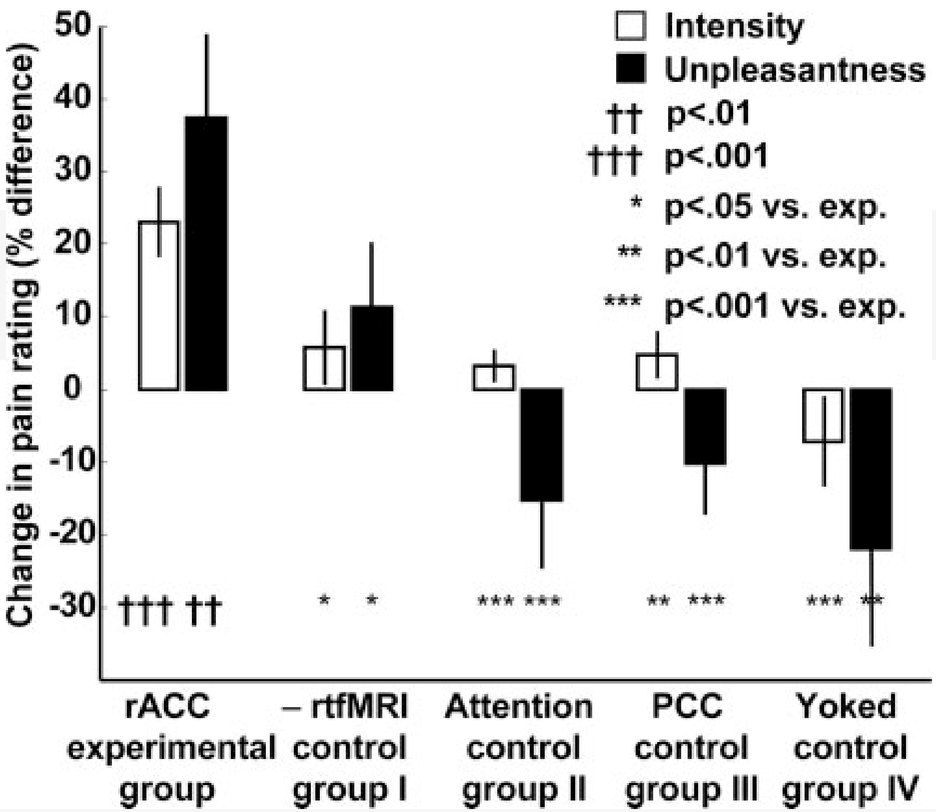


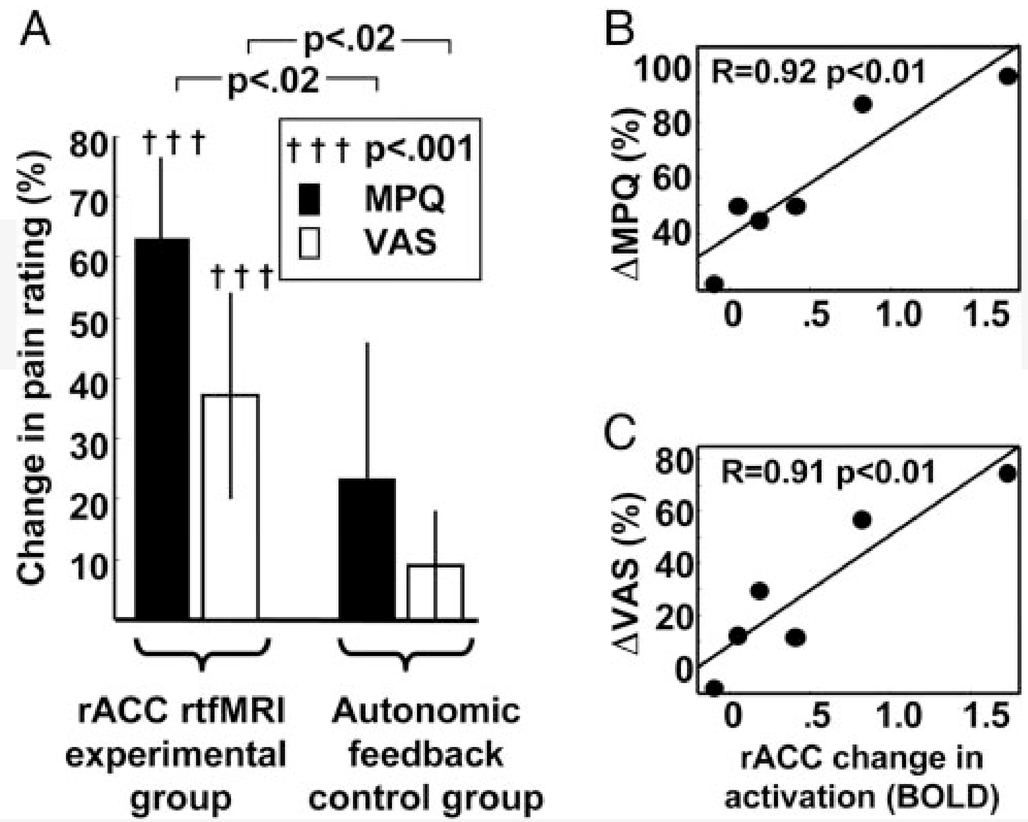
Last Session > First Session

C. deCharms, et al.,
PNAS, 102, 2005

CHANGES in PAIN RATING as a RESULT of RT-fMRI TRAINING

Omneuron





C. deCharms, et al.,
PNAS, 102, 2005

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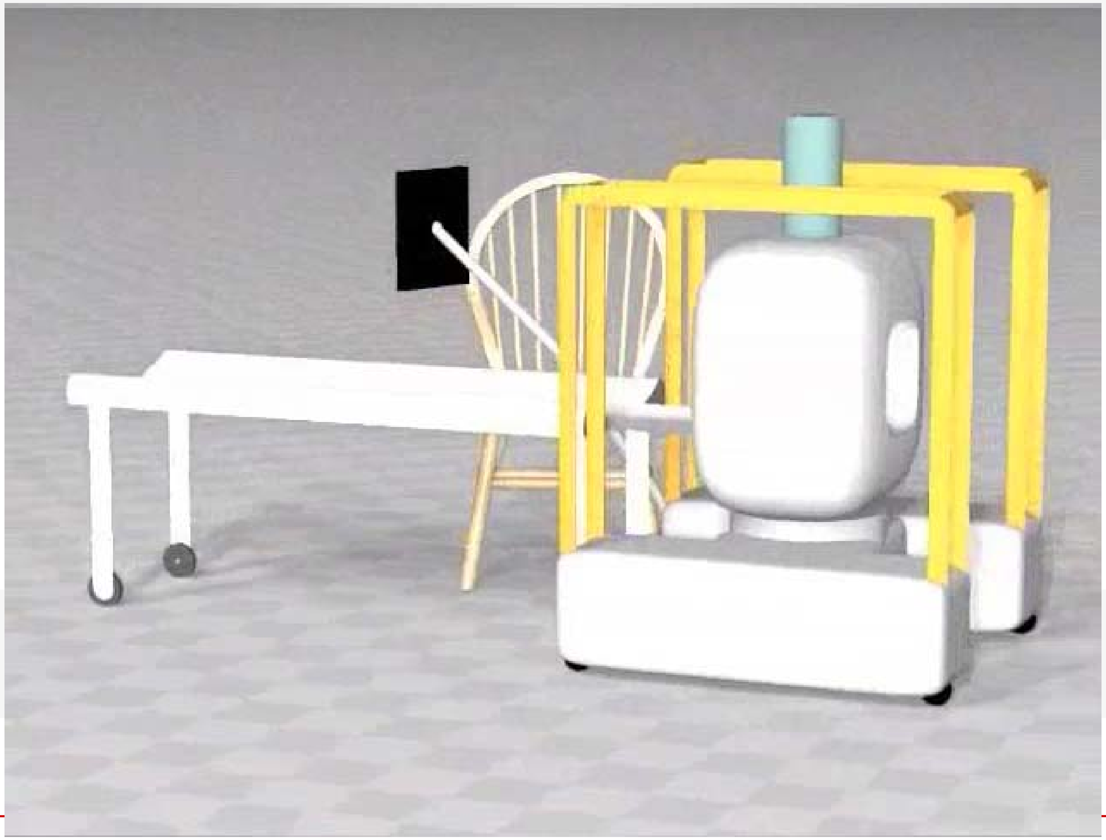
Summary

- Functional Imaging May Provide Unique Opportunities for *Assessing*, *Managing* and *Intervening* in Traumatic Brain Injury
- Dynamic and Real-Time MRI Will Aid in Better Understanding of Pathologies
- MRI Offers Numerous Advantages over CT in Assessment of TBI Sequelae

Summary

- The Availability of Low-Cost, High Performance, Low Field MRI Devices will Improve TBI Management Dramatically.



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- Robin Goldman
- Inseob Hahn
- Alex Korb
- John Stern
- Konstantin Penanen
- Steven Sands
- Manjar Tripathi